

# FINAL REPORT

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## Assessing Risks of Exposure to Plutonium

Part of Task 3: Independent Analysis of Exposure, Dose  
and Health Risk to Offsite Individuals

Revision 2  
February 2000

*Submitted to the Colorado Department of Public Health  
and Environment, Disease Control and Environmental Epidemiology  
Division, Rocky Flats Health Studies in Partial Fulfillment of  
Contract No100APPRCODE 391*

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*"Setting the standard in environmental health"*



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## EXECUTIVE SUMMARY

The Rocky Flats Plant (RFP), located on federal property near Denver, Colorado, operated as a nuclear weapons research, development, and production complex from 1951 through 1989. The Rocky Flats Historical Public Exposures Studies were undertaken to help the Colorado Department of Public Health and Environment evaluate the doses and potential health impacts to the public resulting from contaminant releases from the site to the environment during its years of operation. Phase I of the study was carried out by the ChemRisk Division of McLaren/Hart Environmental Engineering and identified the primary materials of concern, release points and events, quantities released, transport pathways, and preliminary estimates of dose and risk to offsite individuals. The current phase of the study, Phase II, is being performed by *Radiological Assessments Corporation* and involves an in-depth investigation of the potential doses and risks to the public from important historical releases from the RFP. Historical operations at the RFP resulted, amongst other things, in atmospheric releases of plutonium to the surrounding environment. This report examines the data available to quantify the health risk associated with exposure to airborne plutonium and provides central estimates with uncertainties for the organ-specific dose and risk factors. The results from this report are used in the analysis of specific historical plutonium release events from the RFP, which are documented in separate reports.

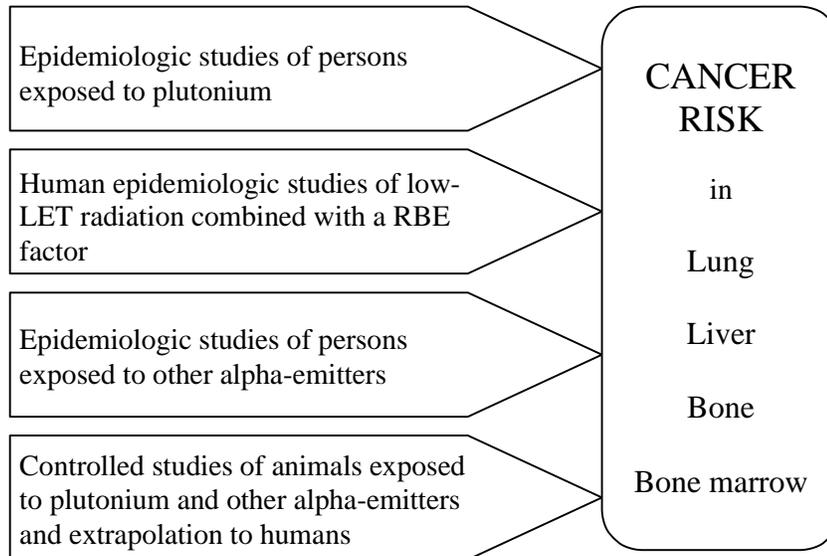
The principal radionuclides of concern at Rocky Flats are  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ , which emit alpha particles and have long half-lives (24,065 and 6,537 years, respectively). Other radionuclides were also released, but they are less important. Plutonium must enter the body before its low penetration high-LET alpha particles can cause biological damage. For historical releases at Rocky Flats inhalation is identified as the primary exposure pathway, and lung, liver, bone, and bone marrow are shown to be the principal organs of concern. The major releases of plutonium to the atmosphere from the Rocky Flats facilities were due to suspension of contaminated soils, releases during two major fires, and routine releases of filtered effluents. Each type of release had different particle size characteristics, but the chemical form is expected to have been mainly the plutonium dioxide. The inhalation dose depends upon the particle size distribution of the plutonium aerosol inhaled. Three different particle size distributions each with a geometric standard deviation of 2.5 are used to account for the range of plutonium particles that individuals could have been exposed to following releases from the site. [Table ES-1](#) summarizes the inhalation dose conversion factors calculated for these plutonium particle size distributions.

**Table ES-1. Dose Conversion Factors for Plutonium Oxide Inhalation**

Cancer site	Dose conversion factor ( $\mu\text{Gy Bq}^{-1}$ ) <sup>a</sup> for plutonium aerosols <sup>b</sup>		
	AMAD = 1 $\mu\text{m}^c$	AMAD = 5 $\mu\text{m}^c$	AMAD = 10 $\mu\text{m}^c$
Lung	4.4 (1.9)	2.6 (2.7)	1.2 (4.3)
Liver	2.0 (3.0)	0.95 (3.5)	0.42 (4.5)
Bone	9.0 (3.0)	4.6 (3.5)	2.1 (4.5)
Bone marrow	0.46 (3.0)	0.22 (3.5)	0.11 (4.5)

<sup>a</sup> To convert the units to mrad  $\text{nCi}^{-1}$ , multiply the values for the geometric mean by 3.7.  
<sup>b</sup> Geometric mean is listed with geometric standard deviation in parentheses.  
<sup>c</sup> Geometric standard deviation of each particle size distribution is 2.5

Making a reliable estimate of the organ-specific cancer risk that results from exposure to plutonium is a major challenge because few human populations have received doses from plutonium that are sufficient to allow the risks to be quantified in an epidemiologic study. In this report, four independent sources of information are used to develop cancer risk estimates with uncertainties for exposure to plutonium (Figure ES-1). These independent cancer risk estimate distributions are then combined to develop an overall cancer risk estimate distribution that takes into account both the uncertainties associated with the estimate, and the intrinsic merit of the approach.



**Figure ES-1.** Combination of four independent approaches to determine the site-specific risk of cancer following plutonium exposure.

The first approach uses the results of epidemiological studies of workers exposed to plutonium in Russia. The workers were exposed to relatively high doses of plutonium and exhibited a statistically significant risk of excess lung cancer. The uncertainties associated with this estimate are examined. The second approach is based on the dose response relationship observed in the Japanese atomic bomb survivors exposed primarily to gamma (low-linear energy transfer [LET]) radiation. These data are the primary source of current risk estimates for ionizing radiation. To apply these risk estimates to plutonium exposures, the difference in effectiveness of alpha radiation (high-LET) compared to gamma radiation to cause biological damage is taken into consideration using the relative biological effectiveness (RBE) factor. The literature is reviewed and organ specific RBE values with uncertainties are derived. The third approach is based on the human dose-response relationships determined for populations exposed to alpha-emitting radionuclides other than plutonium, mainly radon, thorium, and radium. The fourth approach is based on the results of controlled experiments with animals exposed to plutonium and other alpha-emitting radionuclides. In all these approaches, the dose rate and dose levels at which the exposures are received are factors that have to be accounted for in applying them to low dose exposures.

The mortality risk coefficients for each cancer site are adjusted by a lethality fraction to provide lifetime risk coefficients for cancer incidence. Survival data for Colorado are used to determine the lethality fractions. The survival rates for lung and liver cancer are low so there is very little difference between the incidence and mortality risk coefficients. The survival rate for leukemia is also rather low. The median incidence risk coefficient is approximately 25% greater than the mortality risk coefficient. The largest difference is seen for bone cancer where the survival rate is approximately 50%; thus, the median incidence risk coefficient is approximately twice the median mortality risk coefficient. The lifetime cancer incidence risk coefficients with uncertainties for the four primary cancer sites are summarized in Table ES-2.

**Table ES-2. Population Averaged Lifetime Cancer Incidence Risk Coefficients ( $10^{-2} \text{ Gy}^{-1}$ ) For A Population Exposed to Plutonium via Inhalation**

Cancer site	Distribution percentiles <sup>a</sup>
	50 (2.5–97.5)
Lung	14 (1.6–79)
Liver	6.1 (0.85–74)
Bone <sup>b</sup>	0.27 (0.0055–14)
Bone marrow (leukemia)	1.7 (0.042–8.2)

<sup>a</sup> Values reported to 2 significant figures.  
<sup>b</sup> Based on dose to endosteal cells.

This report examines the influence of age and gender on the site-specific risk coefficients. To assess the influence of age, the risk estimates for people under the age of 20 are compared with those for people over the age of 20. A more detailed analysis is not considered justified because of the lack of age-specific risk data for the different cancer sites. Where the difference in the median lifetime risk estimate between those under the age of 20 and those over the age of 20, or between males and females, is judged to be less than a factor of 2 no adjustment is made. This is the case for lung or bone marrow, although the uncertainty in this factor is included in the calculations and leads to some changes in the distributions. For liver and bone, the data suggest that the risks are greater for children than for adults. This is consistent with the age-dependent effect observed for the combined category of all cancers. In our analysis, the median lifetime risk of liver and bone cancer for people under the age of 20 is taken to be twice the median lifetime risk for people over the age of 20. The data also suggest the median lifetime risk coefficients for liver and bone are greater for males than females. The median lifetime risk of liver and bone cancer in males is estimated to be double the median lifetime risk for females. The uncertainties associated with these adjustment factors are incorporated into the calculations. The lifetime cancer incidence risk coefficient distribution for each cancer site depending on age at exposure and gender is presented in [Table ES-3](#). The distributions are approximately lognormal.

The lifetime cancer incidence risk estimates are also presented per unit intake of activity rather than per unit dose. To do this the dose per unit activity (or dose conversion factor) distribution in [Table ES-1](#) is multiplied by the risk per unit dose (risk conversion factor) distribution summarized in [Table ES-3](#) and presented in [Appendix A, Table ES-4](#) summarizes the resulting distributions for 1- $\mu\text{m}$  AMAD plutonium dioxide particles. The risks are presented per 100,000 persons per unit intake of activity in kilobecquerels (kBq). The 2.5 and 97.5 percentile values of the distributions, which are approximately lognormal are given in parentheses.

**Table ES-3. Lifetime Cancer Incidence Risk per Unit Dose ( $10^{-2}$  Gy $^{-1}$ )**

Cancer site	Gender	Lifetime incidence risk distribution percentiles <sup>a</sup>	
		under 20	20 and over
Lung <sup>b</sup>	males/females	13 (1.4–90)	13 (1.4–86)
Liver	males	12 (1.5–150)	6.3 (0.81–80)
	females	5.7 (0.60–80)	3.0 (0.32–41)
Bone	males	0.52 (0.011–29)	0.27 (0.0056–15)
	females	0.25 (0.0052–14)	0.13 (0.0026–7.4)
Bone marrow	males/females	1.7 (0.041–9.3)	1.7 (0.041–8.7)

<sup>a</sup> 50th percentile with 2.5 and 97.5 percentiles of distribution in parentheses, values reported to 2 significant figures.

<sup>b</sup> No account has been taken of the issue of smoking because of lack of information with which to do so.

**Table ES-4. Lifetime Cancer Incidence Risk per 100,000 Persons per Kilobecquerel (kBq) of Inhaled  $^{239}\text{PuO}_2$ , AMAD = 1  $\mu\text{m}$ , GSD = 2.5**

Cancer site	Gender	Lifetime incidence risk <sup>a</sup> ( $10^{-5}$ kBq $^{-1}$ )	
		under 20	20 and over
Lung <sup>b</sup>	males/females	56 (4.1–590)	57 (4.5–570)
Liver	males	25 (1.2–740)	13 (0.62–380)
	females	12 (0.52–360)	6.3 (0.27–190)
Bone	males	4.4 (0.053–450)	2.3 (0.027–220)
	females	2.2 (0.023–230)	1.1 (0.013–120)
Bone marrow	males/females	0.65 (0.0099–15)	0.63 (0.0095–14)

<sup>a</sup> 50th percentile with 2.5 and 97.5 percentiles of distribution in parentheses, values reported to 2 significant figures.

<sup>b</sup> No account has been taken of the issue of smoking because of lack of information with which to do so.

In this report the risks are also calculated for 5- $\mu\text{m}$  and 10- $\mu\text{m}$  AMAD plutonium dioxide particles. The median cancer incidence risk estimates follow the same trends as the 1- $\mu\text{m}$  AMAD aerosols, but are smaller in proportion to the smaller dose conversion factors ([Table ES-1](#)). However, the increased uncertainty in the dose conversion factors for the larger particle size distributions results in large uncertainties in the risk coefficients.

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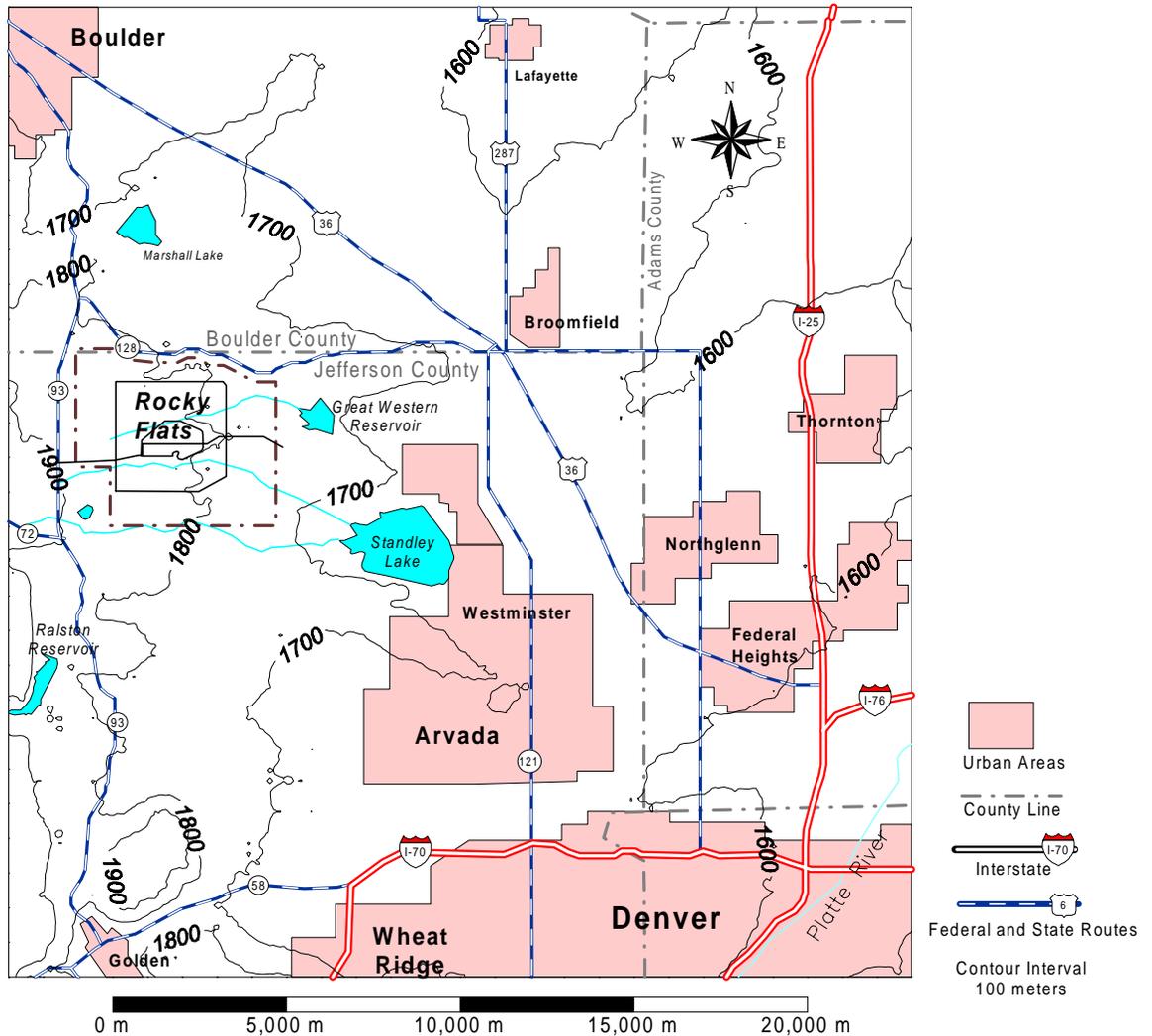
## ACRONYMS AND ABBREVIATIONS

ABCC	Atomic Bomb Casualty Commission
Am	americium
AMAD	activity median aerodynamic diameter
AMTD	activity median thermodynamic diameter
BEIR	Biological Effects of Ionizing Radiation.
Bq	becquerel
CAA	Clean Air Act
CDPHE	Colorado Department of Public Health and Environment
Ci	curie
CI	confidence interval
CV	coefficient of variation
DDREF	dose and dose rate effectiveness factor
DOE	U.S. Department of Energy
DS86	Dosimetry System 1986 (for atomic bomb survivors)
E-A-C	exposure-age-concentration (model)
E-A-D	exposure-age-duration (model)
EAR	excess absolute risk
ELR	excess lifetime risk
ERR	excess relative risk
EPA	U.S. Environmental Protection Agency
eV	electron volt
GI	gastrointestinal
GM	geometric mean
GSD	geometric standard deviation
Gy	gray
HAP	Health Advisory Panel
HEPA	high-efficiency particulate air (filter)
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
ITRI	Inhalation Toxicology Research Institute
kerma	kinetic energy released per unit mass of material
LET	linear energy transfer
LLE	loss of life expectancy

L-Q-E	linear-quadratic-exponential (model)
LSS	Life-span study
m	mean
NAS/NRC	National Academy of Sciences/National Research Council
NCRP	National Council on Radiation Protection and Measurements
NIH	National Institutes of Health
NRC	U.S. Nuclear Regulatory Commission
NRPB	National Radiological Protection Board (United Kingdom)
Pu	plutonium
PuO <sub>2</sub>	plutonium dioxide
PY	person-years
Ra	radium
RAC	<i>Radiological Assessments Corporation</i>
RBE	relative biological effectiveness
REID	risk of exposure induced death
RFP	Rocky Flats Plant
Rn	radon
RR	relative risk
s	standard deviation
Sv	sievert
Th	thorium
T65D	Tentative 1965 Dose (for atomic bomb survivors)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
WL	working level
WLM	working level month

# 1. INTRODUCTION

The Rocky Flats Environmental Technology Site is owned by the U.S. Department of Energy (DOE) and is currently contractor-operated by Kaiser-Hill Company. For most of its history, the site was called the Rocky Flats Plant (RFP) and was operated by Dow Chemical Company as a nuclear weapons research, development, and production complex (Figure 1-1). The RFP is located on approximately 2650 ha (6500 acres) of federal property, within a few miles of the cities of Arvada, Westminster, and Broomfield, Colorado, and 26 km (16 mi) northwest of downtown Denver, Colorado. The production area, now sometimes called the industrial area, is surrounded by a security perimeter fence. The original 156-ha (385-acre) main production area is surrounded by a 2490-ha (6150-acre) buffer zone that now delineates the RFP boundary.



**Figure 1-1.** The location of the Rocky Flats Plant and nearby urban areas in 1980.

## 1.1 The Rocky Flats Historical Public Exposures Studies

Through a 1989 Agreement in Principle between DOE and the State of Colorado, DOE provided the State with funding and technical support for health-related studies. The purpose of the Historical Public Exposures Studies on Rocky Flats is to identify potential health effects in residents in nearby communities who may have been exposed to past toxic and radioactive releases. The Colorado Department of Public Health and Environment (CDPHE) first invited a national panel of experts to help design the health studies. Because of intense public concern about Rocky Flats contamination among Denver metropolitan area residents following a Federal Bureau of Investigation raid of Rocky Flats in June 1989, a Health Advisory Panel (HAP) was established with the responsibility of overseeing the health studies. This panel decided to stress public involvement and to separate the research into two major phases conducted by two different contractors to enhance accountability and credibility.

Phase I of the study was performed by ChemRisk (a division of McLaren/Hart, Environmental Engineering). In Phase I, ChemRisk conducted an extensive investigation of past operations and releases from the RFP. The Phase I effort identified the primary materials of concern, release points and events, quantities released, transport pathways, and preliminary estimates of dose and risk to offsite individuals. The conclusions

**This study focuses on exposure of the public to radioactive and chemical releases from Rocky Flats. A separate joint study between CDPHE and the University of Colorado Health Sciences Center is addressing worker exposures.**

from Phase I were released in a public summary document ([HAP 1993](#)), a series of task reports by ChemRisk, and have since appeared in several articles in the journal *Health Physics*.

*Radiological Assessments Corporation (RAC)* was awarded the contract to conduct Phase II of the study, which is an in-depth investigation of the potential doses and risks to the public from important historical releases from Rocky Flats. Recommendations for work to be performed in Phase II are outlined in the Phase I summary document ([HAP 1993](#)).

## 1.2 Important Sources and Timing of Releases from the Rocky Flats Plant and Global Fallout

For almost 40 years the RFP produced nuclear weapons for national defense. The principal contaminants of concern from past RFP operations identified in Phase I are isotopes of the radioactive element plutonium and the chemical carbon tetrachloride. Possible exposures and risks from another contaminant of concern, beryllium, needed further evaluation in Phase II ([HAP 1993](#)). Plutonium was processed at Rocky Flats for nuclear weapons components. Beryllium, a naturally occurring element, was also used in the nuclear weapons produced at the RFP. Carbon tetrachloride is a solvent that was used to clean plutonium metal parts, processing machinery, and instruments.

To interpret historical measurements of plutonium and related radioactive materials, an understanding of the sources of plutonium in the environment is needed. Two main sources of plutonium in the environment around the RFP are (1) accidental and routine releases from Rocky

**The principal contaminants of concern identified in Phase I are isotopes of the radioactive element plutonium and the chemical carbon tetrachloride ([HAP 1993](#)).**

Flats operations and (2) widely distributed plutonium from the atmospheric testing of nuclear weapons, referred to as global fallout.

Phase I of this study identified the primary events associated with the greatest plutonium releases from the RFP. These were releases from a barrel storage area (the 903 Area), where waste oil containing plutonium leaked from the stored drums and contaminated the soil. Contamination was subsequently transported by wind, especially following removal of the barrels and disturbance of the ground surface. The highest releases occurred during a 5-year period, 1965–1969. An asphalt cover was applied in 1969 to the former barrel storage pad in the 903 Area.

Two other important sources of plutonium releases from the RFP were a major fire in 1957 and resuspension of remaining contaminated soil in the 903 Area in the 1970s.

Revised estimates and uncertainties for these historical releases are being developed in Phase II. However, examining the timing and amounts of plutonium released, according to Phase I results, has provided guidance for interpreting environmental data and allocating resources.

**Global fallout plutonium air concentrations were highest in the early 1960s. Releases of plutonium from Rocky Flats were highest in the late 1960s.**

### 1.3 Phase II Tasks

Phase II of the State of Colorado's studies of health impacts related to the Rocky Flats nuclear weapons plant is designed to provide an independent review of the Phase I research findings and a detailed analysis of the potential health risks from past Rocky Flats contaminant releases. Phase II is divided into six tasks, which are listed below. The first four are technical tasks designed to develop detailed estimates of community exposures and health risks. Task 5 is based on the findings of Task 4 and has been completed. Task 6 allows two-way communication with the community through public meetings, workshops, and other outreach activities to discuss Phase II progress and results.

- Task 1** Coordinate with ChemRisk to ensure quick and efficient access to the records and individuals contacted by ChemRisk during Phase I of the project
- Task 2** Verify the radionuclide and chemical release estimates and associated uncertainties that were developed during Phase I of the project
- Task 3** Conduct an independent assessment of the risks from past Rocky Flats operations using state-of-the-art methods to ensure those risks to the public are carefully identified
- Task 4** Evaluate historical environmental data, which can provide a basis for risk assessment and for reconstruction of releases
- Task 5** Provide recommendations for additional offsite measurements using knowledge gained to ensure that new measurements focus on the most important locations and releases
- Task 6** Provide support for the public involvement efforts.

### 1.4 Task 3: Independent Analysis of the Exposure, Dose, and Health Risk to Offsite Individuals

Task 3 has several parts, including independent analyses of plutonium releases and atmospheric dispersion for exposure assessments. One of these parts (this report) is a special report devoted to evaluating the risk coefficient, i.e., the risk per unit dose (or per unit intake), for plutonium exposure in circumstances when low levels of plutonium are released to the environment, for example at the RFP. The risk coefficient for plutonium is required to convert the dose (or intake) resulting from exposure into health risk.

This report describes and compares four alternative approaches to estimating risk per unit dose. No one of these approaches is fully satisfactory, but each one contributes to the ultimate assessment. Uncertainties in the final determination of the risk per unit dose (or per unit intake) form an important part of the evaluation and provide a measure of the confidence that can be placed in the tissue-specific risk coefficients for plutonium exposure.

### 1.5 Background

Plutonium is a manmade transuranic element produced in nuclear reactors and is an important component of some nuclear weapon systems. The principal radionuclides of concern at Rocky Flats are  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ , which emit alpha particles and have long half-lives (24,065 and 6537 years, respectively [[ICRP 1983](#)]). Plutonium is, therefore, regarded as potentially radiotoxic for very long periods. However, the plutonium must enter the body before its low penetration alpha particles can cause biological damage. After inhalation, the principal organs exposed to plutonium are lung, liver, bone, and bone marrow.

These two isotopes ( $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ ) account for about 93.8% and 5.8% of the mass of the plutonium, respectively. Most of the remaining mass is  $^{241}\text{Pu}$  (0.36%) with a very small amount of  $^{242}\text{Pu}$  (0.03%). The half-life of  $^{241}\text{Pu}$  is 14.4 years. Because of its short half-life, the activity of  $^{241}\text{Pu}$  is greater than that of the other isotopes. One gram of weapons grade plutonium from Rocky Flats contains about 13.69 GBq<sup>a</sup> (0.37 Ci) of  $^{241}\text{Pu}$ , but only a total of 2.66 GBq (0.072 Ci) of  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ . However,  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$  both emit alpha particles and, per unit activity, pose much greater internal exposure hazards than  $^{241}\text{Pu}$ , which emits beta particles. The alpha particle energies of  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$  are nearly identical and cannot be distinguished by alpha spectrometry; therefore, the designation  $^{239,240}\text{Pu}$  is often used to refer to the total activity of the two isotopes. The two isotopes also deliver comparable doses to internal organs after intake. For weapons grade plutonium the dose from  $^{239,240}\text{Pu}$  is about 12 times that from  $^{241}\text{Pu}$ . One atom of  $^{241}\text{Pu}$  decays to one atom of  $^{241}\text{Am}$ , which has a half-life of 432 years. The activity of  $^{241}\text{Am}$  increases with time after chemical separation of the plutonium to a maximum of about 3% of the initial  $^{241}\text{Pu}$  activity 73 years after separation. At that time, the ratio of  $^{241}\text{Am}$  activity to that of  $^{239,240}\text{Pu}$  is about 0.15, and the inhalation dose from  $^{241}\text{Am}$  is about 20% of that from  $^{239,240}\text{Pu}$ . Contributions from americium in-growth to the total dose at earlier times are even smaller.

During past processing at Rocky Flats, plutonium has escaped or been released, contaminating the environment and area close to the Plant. People in the vicinity of the RFP were exposed to this environmental plutonium and retained plutonium in their bodies for many years.

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<sup>a</sup> One gigabecquerel (GBq) is  $10^9$  becquerels or 1,000,000,000 becquerels.

The exposure was mainly via inhalation of plutonium dioxide (see [Table 2-1a](#)). The resulting doses were delivered gradually to the body at a low dose rate. Results produced during Phase I of the Historical Public Exposures Studies, sponsored by the CDPHE ([ChemRisk](#) 1994), suggest that the highest accumulated tissue doses were less than 0.5 mGy (<50 mrad). Doses from the most important releases of plutonium are being independently evaluated as part of the Phase II research, and the estimated tissue doses may change.

The alpha particles emitted from plutonium are densely ionizing and the linear energy transfer (LET) to the tissue is high over the short range (about 40µm) of the alpha particles (thus, the name high-LET radiation). Other radiations, such as gamma rays and x-rays, are less densely ionizing and are termed low-LET radiations. The biological effects of low-LET radiation are better known than those of high-LET radiation. The differences between radiation types are important to the analysis because high-LET radiations are more biologically effective per unit of dose than low-LET radiations. This difference in effectiveness is usually described by the relative biological effectiveness (RBE), which is defined as the ratio of doses from two different radiations to produce the same type and level of biological effect (see the [Glossary](#) at the end of this report).

## 1.6 Plutonium Biokinetics in the Body and Biological Effects

Animal studies have provided information about the kinetics of plutonium translocation from the lung following inhalation exposure and the kinetics and distribution of plutonium to tissues following injection into the blood. After inhalation, plutonium enters the blood mainly from the lung. Results of animal studies that describe the translocation rates and tissue retention times supplement data on tissue distributions found from uptake studies in humans and during human autopsies (see [ICRP](#) 1986).

Current models of plutonium movement within the body after input to the blood ([ICRP](#) 1993a) treat the transport and retention of plutonium to several tissues explicitly. These tissues are bone (including bone surface and bone marrow), liver, kidney, bladder, and gonads. Evidence indicates that about 80% of the plutonium leaving the blood pool goes to either the bone or liver where it is retained for years. Following inhalation of plutonium, the four most highly exposed tissues are bone surface, lung, liver and bone marrow (see [Chapter 2](#)). [Chapter 3](#) discusses in detail the models used to describe transport and retention of inhaled plutonium and the doses that result.

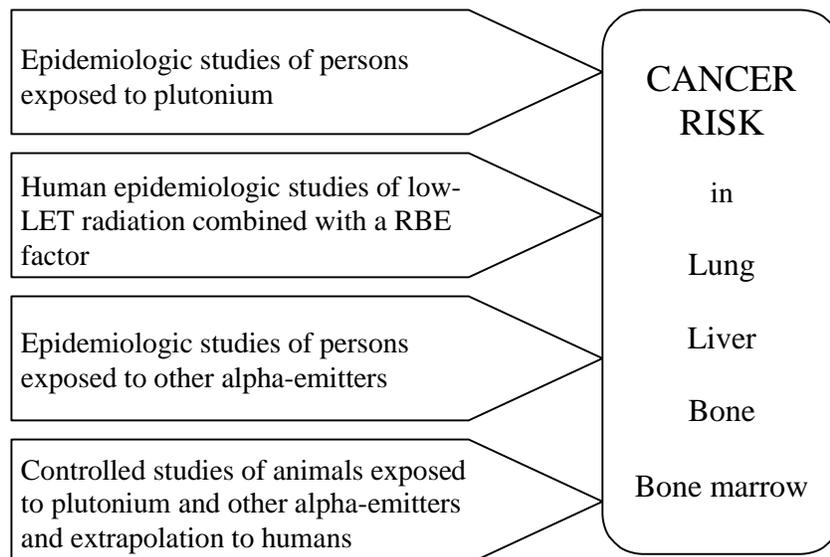
The biological effects produced by low doses (see [Glossary](#)) of plutonium are the risk of induced cancer in the exposed population or the risk of harmful hereditary changes in future generations. These cancers or genetic effects (called stochastic effects) occur randomly in the exposed population. At low doses, only a few individuals will be affected, most will not.

Cancers are most likely to be induced in the organs receiving the most plutonium. The highest doses are expected in the lung, liver, and bone. Doses and risks are calculated for the bone marrow as well. Hereditary or genetic effects depend on the exposure of the gonads (the ovaries in the female, the testes in the male). Because plutonium doses to the gonads are small compared with other organs in the body (40 times less than the lung, see [Table 2-1a](#)) and the risk of genetic effects per unit dose is only about 1/5<sup>th</sup> the risk of cancer induction ([ICRP](#) 1991), genetic effects are not an important risk in this case and are not considered further.

Direct (or deterministic) effects of radiation, such as erythema (reddening of the skin), epilation (loss of hair), impaired fertility, and cataract induction, occur only after threshold doses for these effects are exceeded. In the particular case of plutonium, direct effects include radiation pneumonitis, pulmonary fibrosis, and lymphopenia. The threshold doses are much higher doses (0.5 Gy or more) than those experienced by individuals in the Rocky Flats area (see [Section 1.5](#)). Thus, deterministic effects are not possible in this case and are not considered further in this report.

### 1.7 Approaches to Estimating Risk

Inhalation of plutonium results in exposures of organs to high-LET radiation. While a few human populations have been exposed directly to large amounts of plutonium and some populations to other radionuclides that emit alpha particles, more groups have been exposed to low-LET gamma radiation and have been evaluated in more epidemiologic detail. In addition, there are studies of cancer in animals exposed to both types of radiation and laboratory studies of cellular and other biological endpoints that can be used to support human studies. These different sources of information are used in this study to develop four independent approaches to estimating the risk of cancer due to radiation doses from plutonium deposited in the organs of the human body ([Figure 1-2](#)). Three approaches use epidemiologic studies of human populations to derive dose-response relationships, and the fourth uses dose-response relationships from controlled animal experiments. The following subsections summarize each approach and Chapters [5](#), [6](#), [7](#), and [8](#) describe the approaches in detail. Ultimately, we evaluate these approaches according to their merits and uncertainties, and combine them to produce overall preferred risk coefficients for each relevant organ (see [Chapter 9](#)).



**Figure 1-2.** Approaches to estimating risk coefficients (i.e., risk per unit dose) in various organs or tissues of the body.

### 1.7.1 Epidemiologic Studies of Persons Exposed to Plutonium

The first approach uses epidemiological studies involving human populations exposed directly to airborne plutonium because these are most relevant to exposures at Rocky Flats. These studies include workers exposed to plutonium in defense plants in the U.S. and Russia. The studies of Russian workers are especially valuable because workers were exposed to relatively high doses and had a statistically significant excess of lung tumors. Although there are many uncertainties that must be recognized, dose-response relationships established in such studies are most directly applicable to evaluating risks from Rocky Flats plutonium exposures. [Chapter 5](#) describes this approach.

### 1.7.2 Epidemiologic Studies of Low-LET Radiation Combined with an RBE Factor

The second approach uses knowledge of the consequences of low-LET exposure together with the RBE to account for the relative magnitude of high- and low-LET effects. The principal source of dose-response relationships for human exposure to radiation is from studies of low-LET radiations. Chief among these is the Life Span Study (LSS) of the Japanese survivors of the atomic bombings in Hiroshima and Nagasaki. These survivors were exposed primarily to low-LET gamma rays. (In atomic explosions, both gamma rays and neutrons are released. For the survivors of the atomic bombs dropped at Hiroshima and Nagasaki, the DS86 dosimetry system is used to estimate the doses ([Roesch](#) 1987). In that system, for most of the survivors, 98–99% of the absorbed dose is due to gamma rays and only 1–2% is due to fast neutrons.) The doses were delivered at a high dose rate, almost instantaneously, when the explosions occurred. The risk estimates from the LSS tend to be driven by doses exceeding 1 Gy.

The differences in dose and dose rate and in type of radiation must be considered when using the LSS results to estimate risk factors that would apply to the Rocky Flats long-term plutonium exposures. The differences in effect due to dose and dose rate are reflected in a dose and dose rate effectiveness factor (DDREF). Some information about the DDREF has been obtained by comparing results for atomic bomb survivors with those for groups receiving x- or gamma irradiation over an extended period of time. Some data come from analyses of high and low dose groups of LSS cohort members and from the shape of the dose response curve itself. Dose rate experiments with animals and cells also have contributed to estimates of this parameter.

The difference in cancer induction rates for high- and low-LET radiations is reflected in the RBE of alpha radiation with respect to gamma radiation. This parameter is discussed in detail for each organ of interest (lung, liver, bone, and bone marrow) in [Chapter 6 \(Section 6.4\)](#). Many other factors must also be considered when evaluating the uncertainties in risk coefficients estimated by this approach; [Chapter 6](#) discusses these factors.

### 1.7.3 Epidemiologic Studies of Populations Exposed to Other Alpha-Emitting Radionuclides

The third approach uses human dose-response relationships that have been obtained from studies of populations exposed to alpha-emitting radionuclides other than plutonium. This approach is described in [Chapter 7](#). The radionuclides include radon (Rn) (plus the alpha-

emitting nuclides produced when radon decays) and the isotopes of radium (Ra) and thorium (Th) (see [Glossary](#)). For example, the isotopes of radium include  $^{224}\text{Ra}$ , used clinically to treat certain diseases, and  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ , ingested inadvertently by radium dial painters ([NAS/NRC 1988](#)). To use the results of these studies, the alpha particle RBE is not needed. However, other adjustments may be needed because there are differences in modes of exposure and in the biokinetics and tissue distributions of the various alpha-emitters.

#### **1.7.4 Controlled Studies of Animals Exposed to Plutonium and Other Alpha-Emitters and Extrapolation to Humans**

The fourth approach uses the results of experiments with plutonium and other  $\alpha$ -emitters in animals. This approach is described in [Chapter 8](#). There are obvious disadvantages in using risk estimates that require extrapolation from animals to humans, but animal experiments can provide unique information on both metabolism and effects of plutonium. These studies have been carried out under controlled conditions and were designed to elicit information on the effects of exposure to plutonium at different dose levels. Two types of animal studies are of greatest interest. In the first, the experimental animals were exposed by inhalation to plutonium aerosols at a variety of dose levels. In the second, the experiments were designed to compare the effects of injected plutonium with those of injected radium because the effects of radium in humans were considered relatively well known.

### **1.8 Organization of the Report**

This report focuses on estimating risk coefficients due to irradiation by plutonium of particular tissues in the body especially lung, liver, bone, and bone marrow. The report deals first with plutonium releases and critical groups exposed ([Chapter 2](#)) and then with models of inhalation and metabolism in the body and dosimetry ([Chapter 3](#)). [Chapter 4](#) discusses general epidemiological principles and the bases of risk estimations. Chapters [5](#), [6](#), [7](#), and [8](#) discuss the four specific approaches to risk estimation used in this report and the uncertainties in the risk estimates. The results of these approaches are combined to derive an overall estimate ([Chapter 9](#)) for the risks per unit dose (risk coefficients) as well as risks per unit intake in lung, liver, bone, and bone marrow. Detailed accounting of these risk estimate distributions is provided in the appendix to the report. These risk coefficients are used to quantify the risks for the historical releases at Rocky Flats, the magnitude of which are reported separately. A [reference list](#) and [glossary](#) of terms, which includes an annex of statistical concepts and procedures, complete the report.

## 2. FOCUS OF RISK ASSESSMENT FOR PLUTONIUM RELEASES AT ROCKY FLATS

Key factors affecting the risk assessment are the type and characteristics of releases from Rocky Flats and the behavior of plutonium in the body. The principal RFP releases were due to resuspension of plutonium contaminated soil from the 903 Area and the field to the east, releases to the atmosphere during the fires in 1957 and 1969, and routine discharges. The largest releases were carried by the wind to locations offsite where members of the public were exposed to contaminated air. Other pathways included ingestion of plutonium in water contaminated by liquid discharges from the plant and ingestion of soil, vegetables, or animal products contaminated as the result of deposition of airborne plutonium particles.

In the following sections, we provide an overview of the behavior of plutonium in the body; initial screening estimates of the risks to various tissues; a review of the question of the critical group of exposed persons; and information about the releases of plutonium that were most important to public health.

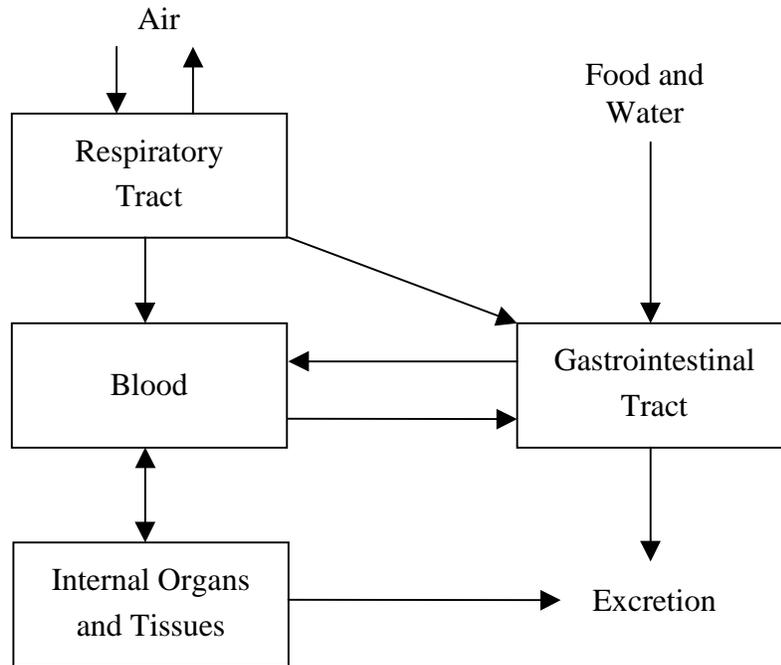
### 2.1 Overview of Plutonium Behavior and Dosimetry Following Intake

Models used for plutonium dosimetry and risk assessment are based upon results of studies of plutonium behavior in both animals and humans. These include measurements of lung deposition and retention, evaluations of uptake to blood from the gastrointestinal (GI) tract, analyses of fecal and urinary excretion observed following exposure, and determinations of the plutonium content of tissues obtained at animal sacrifice or human autopsy. In animal studies, sequential sacrifices provided information on plutonium movement and redistribution in body tissues at various times after exposure. Plutonium can enter the human body in the air that is breathed or in water, food, or soil that enters the GI tract. Another path, primarily related to workplace exposures, is puncture wounds that imbed plutonium in tissue or cuts by sharp objects that are contaminated with plutonium. Once plutonium is inside the body, the blood is the primary fluid that carries it to organs and tissues where it may be deposited and retained. [Figure 2-1](#) shows a very simple box or compartment model of these processes. The arrows indicate the direction of movement of plutonium. [Chapter 3](#) provides diagrams that illustrate more details of the models used for dosimetry. Plutonium in food and water entering the GI tract can be taken up into the blood in the small intestine or passed through in fecal material. Plutonium in air that is breathed is deposited in the respiratory tract or exhaled. From the respiratory tract, the plutonium can travel to the GI tract, to the blood, or to thoracic lymph nodes, which are considered part of the respiratory tract. Plutonium entering the GI tract can be taken up by blood in the small intestine. Plutonium reaching the blood can be deposited in various body tissues or excreted via the kidneys or the lower GI tract.

**Plutonium in the environment can be inhaled or ingested by people. The largest exposures to plutonium around Rocky Flats in the past were due to inhalation of contaminated air.**

Studies of plutonium behavior have led to several important observations that affect elaboration of the simple model in [Figure 2-1](#). The first observation is that little of the plutonium that passes through the GI tract is taken up into the blood. In adults, the uptake fraction is generally considered to be in the range 0.0001–0.0005, although uptake of oxides formed at high temperatures is even lower. Uptake in newborn animals has been shown to be higher by perhaps

a factor of 10, leading to cautiously estimated uptake fractions of 0.001–0.005 for children up to 3 months of age. These uptake fractions, even the estimates for children, are low. The implication of that finding is that exposure pathways involving ingestion of water, soil, and food products are much less important than inhalation.



**Figure 2-1.** Outline of a biokinetic model for plutonium.

Because of the history of plant releases to the atmosphere and the dominance of inhalation over ingestion as a contributor to dose to those residing or working near Rocky Flats, the remainder of this report focuses on the left side of [Figure 2-1](#) and provides details omitted from this simple diagram. The second important observation from plutonium research is that most (~80%) of the plutonium that reaches the blood from the respiratory tract is deposited in the bone and the liver, although the distribution between these tissues varies with age. Thus, bone and liver are clearly tissues that will receive high doses following inhalation of plutonium. A third observation is that plutonium reaching the bone is initially deposited on surfaces and subsequently is slowly translocated into the volume of the bones. This behavior also affects the estimated dose to bone surfaces. A fourth observation is that gonads (testes and ovaries) have been shown to contain concentrations of plutonium that are lower than those in liver but higher than those in other soft tissues. Plutonium retention in the bone, liver, and gonads and plutonium excretion via the kidneys are all modeled explicitly.

The dose coefficients given in [Table 2-1](#) are results of the latest calculations ([ICRP 1995b](#)) and are presented as absorbed dose. The absorbed doses are calculated by dividing the equivalent dose coefficients by an RBE of 20. These are committed doses, which means that, for infants and children, they reflect the total dose received over a 70-year period following an intake. Doses are delivered to the affected tissues at low dose rates over extended time periods. (The units

[ $\mu\text{Gy Bq}^{-1}$  and  $\mu\text{Sv Bq}^{-1}$ ] are those of the *International System of Units* [SI units] with conversion factors to  $\text{mrad nCi}^{-1}$  and  $\text{mrem nCi}^{-1}$  given in [Table 2-1](#) footnotes [a](#) and [f](#).) These dose coefficients reflect the new model for respiratory tract dosimetry (ICRP 1994) and a new biokinetic model for plutonium that has been developed in the past few years (ICRP 1993a). Both of these new models are discussed in detail in [Chapter 3](#).

The table is in two parts: [Table 2-1a](#) contains dose coefficients for plutonium compounds, like the oxide, that are slowly translocated from the respiratory tract to blood. Those people exposed to airborne plutonium from releases from Rocky Flats most likely inhaled the oxide form. [Table 2-1b](#) provides results for plutonium nitrate, whose rate of translocation is classified as moderate. The dose estimates for both chemical forms depend on particle size; estimates in [Table 2-1](#) are for an aerosol with an activity median aerodynamic diameter (AMAD) of  $1\ \mu\text{m}$ . The dose coefficients for  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$  are virtually identical because alpha particles emitted by both long-lived isotopes have very similar energies.

The results of these calculations show that, for adults, the highest doses expected from inhalation of plutonium dioxide ([Table 2-1a](#)) are those to the bone surfaces, followed by doses to the lung, liver, extrathoracic (ET) airways (see [footnote d](#)), red bone marrow, gonads, and kidneys. For adults, the relative magnitudes of the doses are 1, 0.49, 0.22, 0.21, 0.051, 0.013, and 0.0044, respectively. For 3-month-old infants who inhale plutonium dioxide, the highest doses are received by the lung, followed by the extrathoracic airways, bone surfaces, liver, red bone marrow, gonads, and kidneys. For these infants, the relative magnitudes of the doses are 1, 0.69, 0.44, 0.14, 0.041, 0.0088, and 0.0053, respectively. For either adults or infants, the five tissues receiving the highest doses are the two parts of the respiratory tract, the bone surfaces, the liver, and the red bone marrow.

**Aerosols are composed of particles of various sizes. The activity median aerodynamic diameter (AMAD) indicates the central particle size for the distribution.**

The extrathoracic airways are estimated to receive doses that range from 43% (adults) to 58% (infants) of the doses to the lungs. Evidence from follow-up of those exposed to low-LET radiation indicates that the absolute risk per unit dose for the extrathoracic tissues is about 16% of the absolute risk per unit dose for the lung ([Pierce et al.](#) 1996a). Overall, the risk per unit intake for the extrathoracic airways is estimated to range from ~7% (adults) to ~9% (infants) of the risk per unit intake for the lungs. Because our estimate of risk for the lung has a wide range of uncertainty, of which inclusion or exclusion of the extrathoracic airways is only a small part, the extrathoracic airways will not be considered as a separate tissue at risk in this report. This omission is not considered significant for the estimate of risk to the lung.

The next section contains preliminary estimates of the product of the dose factors and the risk factors for induction of cancer. The results provide a preliminary overview of the relative risks to body tissues following plutonium inhalation intakes.

**Table 2-1a. Inhalation Dose Coefficients for  $^{239}\text{Pu}$  or  $^{240}\text{Pu}$  Oxides  
Slow Absorption, AMAD = 1  $\mu\text{m}$  (based on ICRP 1995b, Table 5.29.3c)**

Committed absorbed dose per unit intake ( $\mu\text{Gy Bq}^{-1}$ ) <sup>a</sup>						
Age at intake:	3 months	1 year	5 years	10 years	15 years	Adult <sup>b</sup>
Adrenals	0.034	0.034	0.026	0.019	0.018	0.016
Bladder wall	0.034	0.034	0.026	0.019	0.018	0.016
Bone surfaces	7.0	8.0	8.0	8.0	8.0	9.0
Brain	0.034	0.034	0.026	0.019	0.018	0.016
Breast	0.034	0.034	0.026	0.019	0.018	0.016
GI tract <sup>c</sup>						
Esophagus	0.034	0.034	0.026	0.019	0.018	0.016
Stomach wall	0.034	0.034	0.026	0.019	0.018	0.016
Intestinal walls	0.039	0.038	0.028	0.020	0.018	0.016
Colon	0.040	0.039	0.028	0.020	0.018	0.016
Kidney	0.085	0.085	0.060	0.045	0.042	0.040
Liver	2.3	2.5	2.2	1.8	1.8	2.0
Muscle	0.034	0.034	0.026	0.019	0.018	0.016
Ovaries	0.14	0.16	0.15	0.13	0.13	0.12
Pancreas	0.034	0.034	0.026	0.019	0.018	0.016
Red bone marrow	0.65	0.70	0.50	0.42	0.42	0.46
Respiratory tract						
ET airways <sup>d</sup>	11	9.0	4.6	3.2	1.9	1.9
Lung <sup>e</sup>	16	14	8.5	5.5	4.8	4.4
Skin	0.034	0.034	0.026	0.019	0.018	0.016
Spleen	0.034	0.034	0.026	0.019	0.018	0.016
Testes	0.14	0.16	0.14	0.13	0.13	0.12
Thymus	0.034	0.034	0.026	0.019	0.018	0.016
Thyroid	0.034	0.034	0.026	0.019	0.018	0.016
Uterus	0.034	0.034	0.026	0.019	0.018	0.016
Committed effective dose per unit intake ( $\mu\text{Sv Bq}^{-1}$ ) <sup>f</sup>						
Age at intake:	3 months	1 year	5 years	10 years	15 years	Adult
	43	39	27	19	17	16

<sup>a</sup> Committed doses from age of intake to age 70 for infants and children and over a period of 50 years for adults. To convert the units to mrad  $\text{nCi}^{-1}$ , multiply the values in the table by 3.7.

<sup>b</sup> The biokinetic model for bone applies to ages of 25 and above; committed doses refer to the 50-year period following an intake at age 25.

<sup>c</sup> Gastrointestinal tract; uptake fraction of 0.001 for 3-month-old infants and 0.0001 for other ages.

<sup>d</sup> Dose to tissues of the extrathoracic airways: anterior nose, posterior nasal passages, mouth, pharynx, and larynx.

<sup>e</sup> Dose to thoracic airway tissues: bronchial, bronchiolar, and alveolar-interstitial zones.

<sup>f</sup> See notes a and b above. Effective doses computed using a nominal RBE of 20 for alpha particles. To convert the units to mrem  $\text{nCi}^{-1}$ , multiply the values in the table by 3.7.

**Table 2-1b. Inhalation Dose Coefficients for  $^{239}\text{Pu}$  or  $^{240}\text{Pu}$  Nitrates  
Moderate Absorption, AMAD = 1  $\mu\text{m}$  (based on ICRP 1995b, Table 5.29.3b)**

Committed absorbed dose per unit intake ( $\mu\text{Gy Bq}^{-1}$ ) <sup>a</sup>						
Age at intake:	3 months	1 year	5 years	10 years	15 years	Adult <sup>b</sup>
Adrenals	0.42	0.40	0.26	0.18	0.16	0.14
Bladder wall	0.42	0.40	0.26	0.18	0.16	0.14
Bone surfaces	60	65	60	55	65	75
Brain	0.42	0.40	0.26	0.18	0.16	0.14
Breast	0.42	0.40	0.26	0.18	0.16	0.14
GI tract <sup>c</sup>						
Esophagus	0.42	0.40	0.26	0.18	0.16	0.14
Stomach wall	0.42	0.40	0.26	0.18	0.16	0.14
Intestinal walls	0.43	0.40	0.26	0.18	0.16	0.14
Colon	0.43	0.40	0.26	0.18	0.16	0.14
Kidney	1.1	1.0	0.60	0.42	0.36	0.32
Liver	22	22	20	16	15	16
Muscle	0.42	0.40	0.26	0.18	0.16	0.14
Ovaries	1.2	1.4	1.3	1.2	1.2	1.0
Pancreas	0.42	0.40	0.26	0.18	0.16	0.14
Red bone marrow	8.5	8.0	4.9	3.6	3.3	3.7
Respiratory tract						
ET airways <sup>d</sup>	3.0	2.4	1.2	0.75	0.48	0.45
Lung <sup>e</sup>	7.0	5.5	3.4	2.3	2.0	1.6
Skin	0.42	0.40	0.26	0.18	0.16	0.14
Spleen	0.42	0.40	0.26	0.18	0.16	0.14
Testes	1.4	1.5	1.2	1.0	1.2	1.0
Thymus	0.42	0.40	0.26	0.18	0.16	0.14
Thyroid	0.42	0.40	0.26	0.18	0.16	0.14
Uterus	0.42	0.40	0.26	0.18	0.16	0.14
Committed effective dose per unit intake ( $\mu\text{Sv Bq}^{-1}$ ) <sup>f</sup>						
Age at intake:	3 months	1 year	5 years	10 years	15 years	Adult
	80	77	60	48	47	50

<sup>a</sup> Committed doses from age of intake to age 70 for infants and children and over a period of 50 years for adults. To convert the units to mrad  $\text{nCi}^{-1}$ , multiply the values in the table by 3.7.

<sup>b</sup> The biokinetic model for bone applies to ages of 25 and above; committed doses refer to the 50-year period following an intake at age 25.

<sup>c</sup> Gastrointestinal tract; uptake fraction of 0.005 for 3-month-old infants and 0.0005 for other ages.

<sup>d</sup> Dose to tissues of the extrathoracic airways: anterior nose, posterior nasal passages, mouth, pharynx, and larynx.

<sup>e</sup> Dose to thoracic airway tissues: bronchial, bronchiolar, and alveolar-interstitial zones.

<sup>f</sup> See notes a and b above. Effective doses computed using a nominal RBE of 20 for alpha particles. To convert the units to mrem  $\text{nCi}^{-1}$ , multiply the values in the table by 3.7.

## 2.2 Relative Risks to Tissues Following Inhalation Exposures

The goal of this report is to provide new risk estimates and uncertainties for exposure to plutonium released from the Rocky Flats facilities. It is useful first to make a preliminary assessment of the relative risks for cancer induction following inhalation exposure to plutonium. This initial assessment was completed using a combination of the new International Commission on Radiological Protection (ICRP) respiratory tract and plutonium biokinetic models and the recently revised cancer morbidity risk estimates from the U.S. Environmental Protection Agency (EPA). The EPA tabulation of cancer risks per unit dose is used here because it provides estimates of cancer incidence for many organs and tissues. The following sections describe the EPA risk estimates, provide estimates of the relative risks of cancer, and discuss the results.

### 2.2.1 EPA Estimates of the Risk of Cancer Induction

The EPA has published a new set of radiogenic cancer risk estimates for the U.S. population (EPA 1994; Puskin and Nelson 1995). These results replace earlier estimates by the EPA that were based upon BEIR III (NAS/NRC 1980), a report of the Committee on the Biological Effects of Ionizing Radiations (BEIR) of the National Academy of Sciences/ National Research Council (NAS/NRC). At the request of the EPA and other federal governmental bodies, the Committee has prepared two additional reports: BEIR IV, which deals with alpha-emitters (NAS/NRC 1988), and BEIR V, which focuses upon low-level exposures to photons and the results of the lifespan study of Japanese survivors (NAS/NRC 1990).

The EPA authors also noted that since publication of BEIR III, new assessments of cancer risks have also been issued by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (UNSCEAR 1988), by the National Radiological Protection Board (NRPB) in the United Kingdom (Stather et al. 1988), by the ICRP (ICRP 1991; Land and Sinclair 1991; Upton 1991), and by the U.S. Nuclear Regulatory Commission (Gilbert 1991, 1993). They considered these sources in addition to the BEIR reports as part of their review and new assessment.

Table 2-2 contains the EPA estimates of cancer mortality and morbidity due to radiation exposure of the U.S. population and, for reference, the mortality risks based upon BEIR III that were used previously to implement the Clean Air Act (CAA) (EPA 1989). The values in the table are for low doses, <0.2 Gy (<20 rad), from radiations with low (<0.5 keV  $\mu\text{m}^{-1}$ ) linear energy transfer (LET) rates delivered at low dose rates, 0.1 mGy  $\text{min}^{-1}$  (<10 mrad  $\text{min}^{-1}$ ). Note that the EPA report stated that “the number of significant figures should not be considered to indicate the level of certainty in the tabulated values” (EPA 1994).

For the induction of cancer in most tissues, the EPA estimates risks from high-LET radiations using a relative biological effectiveness (RBE) of 20 and a dose and dose rate effectiveness factor (DDREF) of 2 for low doses and dose rates. For leukemia and breast cancer, the RBE values are taken to be 1 and 10,<sup>b</sup> respectively, independent of dose and dose rate. The EPA values of RBE and DDREF have been employed in the calculations summarized below. Differences between low- and high-LET radiations and the range of RBE values and uncertainties for particular tissues are discussed in Chapter 6, Section 6.4.

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<sup>b</sup> 10 for breast cancer because EPA used a DDREF of 1 not 2 for breast cancer (see Section 6.4.5 also).

**Table 2-2. EPA Low Dose, Low Dose Rate Cancer Mortality and Morbidity Risks Per Unit Absorbed Dose of Low-Linear Energy Transfer Radiation**

Cancer site	Cases per 10 <sup>4</sup> P-Gy (or per 10 <sup>6</sup> P-rad)		
	Mortality		Revised morbidity
	CAA <sup>a</sup>	Revised	
Esophagus	9.1	9.0	9.5
Stomach	46.0	44.4	49.3
Colon	22.9	98.2	178.5
Liver	49.6	15.0	15.8
Lung	70.1	71.6	75.4
Bone	2.5	0.9	1.3
Skin	<sup>b</sup>	1.0	1.0
Breast	55.4	46.2	92.5
Ovary	<sup>b</sup>	16.6	23.7
Bladder	11.8	24.9	49.7
Kidney	5.0	5.5	8.4
Thyroid	6.4	3.2	32.1
Red bone marrow	44.8	49.6	50.1
Remainder	67.8	123.1	173.4
Total	392.1	509.1	760.6

<sup>a</sup> Values previously used in Clean Air Act assessments ([EPA](#) 1989).

<sup>b</sup> No value given.

### 2.2.2 Relative Risks of Cancer Incidence in Tissues

If we symbolize the risk factor for incidence of malignancy per unit RBE-weighted absorbed dose in a particular tissue ( $T$ ) by  $I_T$  and the RBE-weighted absorbed dose to that tissue by  $D_{RT}$ , then the fraction of the total morbidity risk associated with tissue  $T$  is  $(D_{RT}I_T)/(\sum D_{RT}I_T)$ . To make the calculations, we employed absorbed dose factors from [Table 2-1](#), weighted by the RBEs used by the EPA, and the low-LET risk factors from [Table 2-2](#). These computed ratios are a guide to the most important tissues for our work. However, our analysis of the RBEs is more detailed and differs from that of the EPA (see [Chapter 6](#)).

**The relative biological effectiveness (RBE) of alpha radiation for cancer induction is a measure of the greater risk of disease per unit dose than would be produced by the reference gamma radiation.**

[Table 2-3](#) gives results of calculations of the morbidity risk fractions for adults. The largest risks are associated with the lung, liver, and bone surfaces. These three tissues account for nearly 98% of the total risk of cancer induction for infants inhaling plutonium and about 96% of the total cancer risk to adults. For adults, estimated risks of colon and ovarian cancer and of leukemia are comparable, each accounting for 0.6–0.8% of the total cancer risk. These same sites account for most of the residual risk in infants. The nine so-called remainder tissues together account for 0.5–0.7% of the total risks for infants and adults.

**Table 2-3. Contributions of Tissues to Total Morbidity  
Due to Inhalation of <sup>239</sup>Pu or <sup>240</sup>Pu in Oxide Form**

Organ or tissue	$(D_{RT} I_T) / (\sum D_{RT} I_T)$	
	Infant (3-months)	Adult
Esophagus	0.00026	0.00039
Stomach	0.0013	0.0020
Colon	0.0058	0.0075
Liver	0.029	0.080
Lung	0.94	0.85
Bone surface	0.0073	0.031
Skin	0.000027	0.000042
Breast	0.0025	0.0038
Ovary	0.0027	0.0074
Bladder	0.0013	0.0020
Kidney	0.00057	0.00087
Thyroid	0.00087	0.0013
Red bone marrow	0.0026	0.0059
Remainder <sup>a</sup>	0.0050	0.0068

<sup>a</sup> Comprised of adrenals, brain, upper large intestine, small intestine, muscle, pancreas, spleen, thymus, and uterus.

### 2.3 Definition of the Critical Group on the Basis of Age and Activity

An important question in any risk assessment is the definition of the critical group, that is, those individuals whose location, age, habits, or other factors cause their risk to be highest. It is of particular interest to determine whether risks to infants and young children, who may have been exposed to airborne plutonium due to past routine releases, accidents, or resuspension of contaminated soils, exceed those of adults similarly exposed. In the first part of the analysis, the effect of location is not considered because it is dependent primarily upon atmospheric dispersion patterns. In [Section 2.3.1](#), we consider people of a variety of ages, living in the same home or neighborhood, that could have been exposed to comparable outdoor and indoor concentrations of plutonium. In [Section 2.3.2](#), we examine the dependence of the risk estimates on age and gender.

#### 2.3.1 Dependence of Intakes and Doses on Age

For exposure to a plutonium aerosol at a particular location, two factors change markedly with age: breathing rate and committed effective radiation dose per unit intake of activity. The dose coefficients reflect differences in lung deposition, which change with breathing rate and lung dimensions. We use the committed effective doses, listed at the bottom of Tables [2-1a](#) and [2-1b](#), as preliminary surrogates for the risk of the radiation exposure because they include contributions from all organs and general measures of the radiosensitivity of irradiated tissues within the body. Further analysis of the risks to the most important individual tissues following plutonium inhalation is the goal of this report.

The age-dependent breathing rates and effective dose coefficients and their products, the risk per unit time-integrated air concentration (Bq d m<sup>-3</sup>), are presented in [Table 2-4](#) for several

ages and two absorption types for plutonium. The effective dose per unit intake of activity generally decreases with age, while the opposite is true of the breathing rate. The product, which is used as a surrogate measure of risk, is greatest for an adult doing heavy labor during the exposure.

**Table 2-4. Preliminary Surrogate Risk Estimates**

Age	Breathing rate <sup>a</sup> (m <sup>3</sup> d <sup>-1</sup> )	Effective dose <sup>b</sup> (mSv Bq <sup>-1</sup> )		Surrogate risk estimate <sup>c</sup> [mSv (Bq d m <sup>-3</sup> ) <sup>-1</sup> ]	
		Type M	Type S	Type M	Type S
3 months	1.6	0.080	0.043	0.13	0.069
1 year	5.1	0.077	0.039	0.39	0.20
5 years	8.7	0.060	0.027	0.52	0.23
10 years	15.3	0.048	0.019	0.73	0.29
15 years	17.7	0.047	0.017	0.83	0.30
Adults		0.050	0.016		
Sedentary	20.7			1.0	0.33
Laborer	26.8 <sup>d</sup>			1.3	0.43

<sup>a</sup> Averages for males and females from [Roy and Courtay](#) (1991)

<sup>b</sup> From Table 2-1 compiled from ICRP Publication 71 ([ICRP](#) 1995b); absorption types: moderate (M), slow (S).

<sup>c</sup> The effective dose per unit time integrated air concentration.

<sup>d</sup> Male value only.

For Type S, slowly absorbed plutonium (oxides), the surrogate risk estimates for ages 10, 15, and for sedentary adults are practically identical and are about 1.5 times higher than the risk for age 1 and slightly more than 4 times higher than the risk for newborn children. For Type M, moderately fast absorption, there is a broader range of values and an even greater difference between values for adults and infants. [Morgan et al.](#) (1992) estimated that doses received *in utero* are substantially less than those received by the mother.

The surrogate risk estimates given in [Table 2-4](#) do not consider the effect of being inside a dwelling or other building. Based upon comparative measurements, the indoor concentrations of environmental pollutants were found to be ~1.5 times lower than those in the outdoor environment at the same time and location ([Andersen](#) 1972). People engaged in manual labor and those with other occupations that require substantial outdoor work would generally be exposed to higher air concentrations. Infants and young children would be more likely to be exposed to the lower air concentrations found indoors.

### 2.3.2 Dependence of Risk Factors on Age and Gender

The use of effective dose as a surrogate for risk, as in [Table 2-4](#), assumes that there are no differences in sensitivity to radiation exposure for the various ages. For the primary source of data, the lifespan study of the atomic bomb survivors, all the data are not yet available to answer this question because follow-up of all those exposed as children is not yet complete. However, it is generally observed that the youngest exposed age groups are more sensitive to cancer induction by ionizing radiation.

Greater sensitivity of younger people seems to be well documented for the category of all cancers in the lifespan study of atomic bomb survivors (see [Chapter 4, Table 4-4](#)) and for some selected sites, such as female breast ([UNSCEAR 1994](#); [NAS/NRC 1990](#)) and thyroid ([Ron et al. 1995](#)). However, for lung cancer alone (among the more common sites of radiation-induced cancer), the age dependence seems to be different. The risk of lung cancer shows little dependence on age for either the Japanese survivors or the studies of exposure to alpha-emitting radon decay products. If there is a difference, it may be that the young are less sensitive than the old (see [Section 4.6](#)).

Another large contribution to the total risk comes from liver cancer. Studies of the induction of liver tumors following injections of radioactive thorium as Thorotrast do not indicate an effect related to age at injection ([Van Kaick et al. 1989](#); [Andersson et al. 1994](#)). In those studies, the dose to the liver was primarily from alpha particles. For low-LET radiation, however, the risk of tumors of the digestive tract is greater at ages less than 20 than for older persons ([NAS/NRC 1990](#)). [UNSCEAR \(1994\)](#) gives specific estimates for liver cancer from the study of the atomic bomb survivors (Table 8, Part IV). The estimates of absolute risk for people who were under age 20 are about twice those for people over age 20 at the time of exposure. For liver cancer, it is considered that those under age 20 may be twice as susceptible as people over age 20 (see [Section 4.6](#)).

The third major component of the risk from plutonium inhalation is bone cancer. As for liver cancer, the results for studies of high- and low-LET radiation differ. [Mays and Spiess \(1983\)](#) studied bone cancer in patients given repeated injections of  $^{224}\text{Ra}$  as a medical treatment. They found no difference in bone cancer risk between those exposed as adults and those exposed as juveniles or between males and females. As noted elsewhere (see [Section 7.3.3](#)),  $^{224}\text{Ra}$  is similar to  $^{239}\text{Pu}$  in that both nuclides deliver relatively high doses to bone surfaces. A follow-up analysis documented in [Chmelevsky et al. \(1986\)](#) found no difference in tumor rates between the two age groups. For acute exposure to low-LET radiation, the limited data, which is summarized in the latest UNSCEAR report ([UNSCEAR 1994](#)), suggest that males may be three times more sensitive than females and that those under age 20 may have risks that are three times greater than those over age 20. Although the total number of cases was small, it is considered reasonable to allow for a possibly higher sensitivity in those under 20 years of age. A factor of 2 greater sensitivity for that group is recommended in [Section 4.6](#).

Leukemia is not expected to be one of the primary outcomes of plutonium exposure (see [Table 2-3](#)), but the estimates in Table 4-3 of the BEIR V report ([NAS/NRC 1990](#)) show that for exposure at ages 5 and 15, the risks are between two and three times higher than for ages 25 and 35. However, adults become more sensitive at older ages ([Upton 1991](#)) with a net result that, when compared to all adults (Table 8, Part XII), those under age 20 are slightly less sensitive to leukemia induction ([UNSCEAR 1994](#)).

The effect of gender on cancer risk estimates is addressed in [Chapter 4](#). Considering both the studies with other alpha-emitters and the study of the Japanese survivors, it is appropriate to allow for a higher sensitivity to liver and bone cancer induction in males. Accordingly, risks for liver and bone cancer induction in males are taken to be twice those in females ([Section 4.7](#)).

### 2.3.3 Summary

The calculations discussed in [Section 2.3.1](#) indicate that the level of activity and exposure outdoors are more important than age as determinants of risk from inhalation of releases from Rocky Flats. Most of the total risk is due to induction of lung cancer; liver and bone cancer are the next most important effects. Lung cancer risks do not appear dependent upon either age at exposure or gender; however, liver and bone cancer risks are considered to depend upon both age and gender. For persons under age 20, liver and bone cancer risks are estimated to be twice those for adults. Males are estimated to be twice as sensitive as females for liver and bone cancer induction. Because liver and bone cancer make relatively small contributions to the total risk (see [Table 2-3](#)), age and gender differences do not greatly affect the surrogate estimates of risk in [Table 2-4](#). The estimated risks for young males would be about 20% higher than the values in the table.

Active males who spent considerable time outdoors would be the group at highest risk from Rocky Flats plutonium releases. Age is relatively unimportant, although it changes the likelihood of a person being at a location where plutonium air concentrations were high. To illustrate, although adult ranchers have worked outside near the RFP boundary, it is unlikely that children would have been similarly exposed with the same regularity.

The points of highest potential exposure differ for the different releases. For example, air concentrations were highest near the eastern plant boundary following suspension of plutonium from the 903 Area. Locations of maximum air concentrations during the fires depend upon the winds at the time of these events, while the routine releases were dispersed over a much wider area.

## 2.4 Important Characteristics of Releases to the Atmosphere

Because inhalation is the route of exposure of concern in this analysis, this section reviews information about the plutonium aerosols that were released and subsequently available for inhalation. The most important attributes of those aerosols are the particle size and chemical form. The calculations presented above assumed that the inhaled aerosol had an AMAD of 1  $\mu\text{m}$ . This particle diameter is often used for reference calculations, but the actual doses depend upon the particle size distribution of the particular aerosol inhaled.

As noted above, the major releases of plutonium to the atmosphere from the Rocky Flats facilities were due to suspension of contaminated soils, releases during two major fires, and routine releases of filtered effluents. Each type of release had different particle size characteristics, but the chemical form of all of these releases is expected to have been mainly plutonium dioxide. Available particle size information for each of these three release categories is discussed in the following sections.

### 2.4.1 Releases from 903 Area

Measurements of the particle size of material made airborne by mechanical disturbance or high winds were not performed until after 1970. By that time, the initial source of contamination had been covered by an asphalt pad. Resuspension of contaminated soil to the east of the pad was the primary source of airborne material.

In 1973, measurements of plutonium in airborne dust were made at three heights above the ground at the east security fence and about 350 m (1150 ft) further east ([Sehmel and Lloyd 1976](#)). Detailed breakdowns of the size distributions were not obtained, but AMADs of the resuspended particles were between 2 and 7  $\mu\text{m}$ . Geometric standard deviations (GSDs) appear to have been  $\sim 2$ , but they were not clearly defined in all cases. The physical diameters of plutonium particles on air filters collected by Sehmel and in two soil samples were measured by [Hayden](#) (1976) using a fission track method. The particles on the air filters were found to have physical diameters of 0.08  $\mu\text{m}$ , which correspond to an AMAD of about 0.27  $\mu\text{m}$ . This diameter is substantially lower than that of the soil particles to which the plutonium particles were attached.

Physical diameters of plutonium particles in a soil sample from the original contaminated area were found to range up to about 1  $\mu\text{m}$ , with a mean of 0.3  $\mu\text{m}$  (AMAD  $\sim 1$   $\mu\text{m}$ ). That sample was taken from beneath the asphalt pad at the 903 Area. A second soil sample collected downwind of the 903 Area was found to contain particles with mean physical diameter of 0.08  $\mu\text{m}$  (AMAD  $\sim 0.3$   $\mu\text{m}$ ). Thus, it would appear that the airborne plutonium particles were attached to soil particles.

[Krey et al.](#) (1976) estimated the respirable fractions of the airborne plutonium activity using measurements made with an elutriator and cascade impactors. They compared the amount of airborne plutonium associated with particles  $< \sim 8$   $\mu\text{m}$  in diameter with the total activity and estimated that  $23 \pm 19\%$  (mean  $\pm$  standard deviation) of the airborne activity in their elutriator samples was respirable. That is, that fraction of the airborne particles could have entered the respiratory tract during breathing. Data from the elutriator yielded a broad range of respirable fractions. Their results indicate that between 16% and 58% of the particles could have entered the respiratory tract. Using data from impactors, they found average respirable activity fractions in the range 16% to 82%, with a central value of  $45 \pm 21\%$ .

The measurements made near Rocky Flats are consistent with those found in other locations. [Dorrian](#) (1997) reviewed measurements of particle size distributions for environmental aerosols. She found a median AMAD of 6  $\mu\text{m}$  for results of 16 measurements of aerosols arising from resuspension. The range of observed values given was from 1 to 15  $\mu\text{m}$  and the GSD of the cumulative distribution was 1.9.

#### **2.4.2 Filtered Releases from Routine Processing and Operational Accidents**

Studies of aerosols in work areas within plutonium facilities have shown aerosol AMADs in the range 0.1–20  $\mu\text{m}$  ([Moss et al.](#) 1961; [Anderson](#) 1964; [Kirchner](#) 1966; [Elder et al.](#) 1974; [Hayden](#) 1976). These values are typical of the aerosols found in exhaust air streams before the exhaust filtration system. [Dorrian and Bailey](#) (1995) conducted an extensive review of particle size distributions in the workplace. Of their categories, fuel handling facilities, which included both uranium and plutonium plants, are most similar to Rocky Flats operations. For 57 measurements, the observed range of AMADs was from 0.34–16  $\mu\text{m}$ . The median particle size for the composite distribution was 3.8  $\mu\text{m}$ , with a GSD of 1.8.

Discharges of airborne effluents from the plutonium buildings passed through one or more sets of high-efficiency particulate air (HEPA) filters before release to the environment. Routine releases followed this path, as did releases that occurred following most of the incidents and accidents involving plutonium within the facilities.

[Hayden](#) (1976) also reported that plutonium particle sizes measured in stack effluent air had median physical diameters of 0.09  $\mu\text{m}$ , corresponding to an AMAD of 0.3  $\mu\text{m}$  for plutonium dioxide, with a GSD of 1.6. A range of particle sizes was found for glovebox aerosols and for components of surface contamination in the facility. [Hayden](#) (1976) noted that the observed median AMAD was comparable to that expected to most effectively penetrate the HEPA filters that were used.

### **2.4.3 Releases from the 1957 Fire**

During the 1957 accident, the fire spread through the glovebox exhaust ventilation system, burned through the set of glovebox exhaust filters, and subsequently burned many of the filters in the building exhaust air filtration system. No data are available on the particle size of the plutonium aerosols released to the atmosphere during this event. A study of the aerosols from another Rocky Flats fire involving plutonium and solvents showed that the particles produced were quite small. Three samples collected between 4.6 m (15 ft) and ~15 m (50 ft) gave similar results. The composite AMAD for the three aerosol samples was 0.32  $\mu\text{m}$  and the GSD was 1.83 ([Mann and Kirchner](#) 1967). Estimates of releases for the 1957 fire ([Voillequ e](#) 1999) are based upon the respirable fractions of aerosols produced by oxidation of the plutonium and burning of contaminated filters. A broad range of respirable particle sizes is considered.

### **2.4.4 Releases from the 1969 Fire**

No measurements of particle size are available for releases from the 1969 fire. During this event, the main building ventilation exhaust system (one stage of HEPA filtration) was not severely damaged. Two supplementary (booster) exhaust systems (having four to six stages of HEPA filtration) also discharged from the building to the atmosphere. Both systems served glovebox lines where the fire damage was most severe. Filters in one of these systems (Booster System #2) were plugged by smoke early in the fire and most glovebox air was carried by Booster System #1. All filter stages in this system were damaged and their partial failure led to the bulk of the release during the fire. The discharge was via a duct that faced down toward the roof of the building. Significant deposition, presumably of larger particles, occurred on the roof and nearby ground surfaces.

### **2.4.5 Summary of Particle Size Information**

For the largest release, from the 903 Area, it appears that an aerosol with an AMAD of ~5  $\mu\text{m}$  and GSD of ~2.5 would span the range of plutonium bearing dust particles to which a person would have been exposed. For routine vent and stack effluents that were effectively filtered, an AMAD of ~0.3  $\mu\text{m}$  is most appropriate; however, when filter leakage occurred, larger particles (more typical of the workplace aerosols) would have been released. For these releases, an aerosol with an AMAD of ~1  $\mu\text{m}$  and GSD ~2.5 is considered to be a reasonable approximation of the composite aerosol. For the two fires, a broader range of AMADs must be considered because of the lack of information. Three aerosols, with AMADs of 1, 5, and 10  $\mu\text{m}$ , were selected for this analysis. Each is assumed to contain a relatively broad distribution of particle sizes (GSD ~2.5).

## 2.5 Conclusions

The most important pathway for exposure of the public living or working in the vicinity of the Rocky Flats facility was inhalation of plutonium particles. The largest source of these particles was disturbance, suspension, and resuspension of contaminated soils in the 903 Area. There were other releases directly to the atmosphere from stacks and vents during routine operations and two major fires. The characteristics of the plutonium aerosols are important for assessing the doses and risks to people exposed.

For people exposed to the Rocky Flats plutonium aerosols, the tissues that will receive the highest doses and the highest risks of cancer induction following exposure are lung, liver, and bone. A preliminary evaluation using EPA risk factors indicates that these three tissues account for about 96% of the total risk of cancer induction in persons exposed as adults and about 98% of the total for those exposed as infants.

Considering age-dependent factors, typical activities, and relative cancer risks leads to the conclusion that males, aged 15–20 years, working or vigorously exercising near the facility during periods of the highest releases would have received the highest doses and been exposed to the highest risks. The most important effect of age is its influence on lifestyle and the likelihood of being at a point of high plutonium air concentration. For releases from the 903 Area, maximum doses and risks will not be underestimated by considering a critical group of young men who were physically active or routinely performed strenuous labor outside near the plant. Similarly, members of that group were more likely to have been outside on the night of the 1957 fire.

The aerosols to which the critical group was exposed varied with the release point. For the 903 Area, small plutonium particles were attached to larger dust particles with a broad range of sizes. These are characterized using an AMAD of 5  $\mu\text{m}$  and a GSD of 2.5. For routine releases, particle sizes were smaller, with an AMAD of  $\sim 1$   $\mu\text{m}$  and a GSD of 2.5. The sizes of particles released during the fires are not known because measurements were not made. Aerosols with AMADs of 1, 5, and 10  $\mu\text{m}$ , each with a GSD of 2.5, will be addressed to cover a broad range of possible particle sizes in those discharges.

### 3. PLUTONIUM BIOKINETIC MODELS AND DOSIMETRY

This chapter discusses in some detail the models used to estimate radiation doses following inhalation of particles containing plutonium. Readers interested primarily in plutonium risk estimates may prefer to read only the introductory material (Sections [3.1](#) and [3.2](#)) and the summary ([Section 3.7](#)). [Section 3.2](#) is an overview of plutonium behavior in the body. [Section 3.3](#) considers the deposition of particles containing plutonium in and their clearance from the respiratory tract. [Section 3.4](#) presents models of plutonium transport to other body tissues. [Section 3.5](#) presents basic dosimetric principles and [Section 3.6](#) discusses uncertainties in the dose coefficients.

#### 3.1 Introduction

Evaluating the radiation doses received by tissues in the body following intake is an essential step in assessing risks from plutonium. The dose evaluation procedure requires models of the behavior of plutonium that has been inhaled or ingested. The models are generally termed biokinetic rather than metabolic because plutonium is not a normal component of human metabolism. It is important to understand the movement of plutonium within the body because the organs and tissues in which it deposits and is retained are exposed to the alpha particle emissions of the important plutonium nuclides.

[Section 3.2](#) discusses general features of the behavior of plutonium taken into the body. Subsequent sections discuss models that are particularly relevant to exposure to plutonium released from Rocky Flats.

#### 3.2 Overview of Plutonium Behavior Following Intake

The biokinetic models used for plutonium dosimetry are based upon measurements of plutonium behavior in both animals and humans. These include measurements of lung deposition and retention, studies of uptake to blood from the GI tract, analyses of data on fecal and urinary excretion following exposure, and determinations of the plutonium content of tissues obtained at animal sacrifice or human autopsy. In animal studies, sequential sacrifices provided information on plutonium movement and redistribution in body tissues at various times after exposure.

Plutonium can enter the human body in the air that is breathed or in water, food, or soil that enters the GI tract. Other modes of entry, of particular concern in industrial situations, are puncture wounds that imbed plutonium in tissue and cuts by sharp objects that are contaminated with plutonium. Once plutonium is inside the body, the blood is the primary fluid that carries it to organs and tissues where it may be deposited and retained. [Figure 2-1](#) (presented earlier) shows a very simple box or compartment model of these processes. The arrows indicate the direction the material is transferred. (All possible transfers are not shown in that simple diagram.) Plutonium in food and water entering the GI tract can be taken up into the blood in the small intestine or passed through in fecal material. Plutonium in air that is breathed is deposited in the respiratory tract or exhaled. Plutonium can be cleared from the respiratory tract to the blood or to the GI tract. Plutonium reaching the blood can be deposited in

**Models of plutonium behavior in humans are based upon animal research and human studies, which include evaluation of occupational exposure cases.**

various body tissues or excreted via the kidney or the GI tract. [Section 3.3](#) describes the details of the respiratory tract models, which are most important for exposures to Rocky Flats releases.

Studies of plutonium behavior have led to several important observations that have guided elaboration of the model in [Figure 2-1](#). The first observation is that little of the plutonium that passes through the GI tract is taken up into the blood. In adults, the uptake fraction is in the range 0.0001–0.0005. An uptake fraction of 0.0005 means that 5 parts in 10,000 will enter the blood stream from the GI tract. Uptake in newborn animals has been shown to be higher by perhaps a factor of 10, leading to a range of estimated uptake fractions of 0.001–0.005 for children up to 3 months of age. The second observation is that most (~80%) of the plutonium that reaches the blood is deposited in the bone and the liver. The fractions of plutonium reaching these two tissues vary with age, but bone and liver are clearly tissues that will receive high doses. A third observation is that gonads (testes and ovaries) have been shown to contain somewhat elevated concentrations of plutonium. Like bone and liver, these tissues are modeled explicitly. Other tissues do not stand out as sites of deposition, but evidence indicates that clearance rates for plutonium reaching soft tissues vary. This leads to the use of multiple soft tissue compartments in a more detailed biokinetic model. That model is described in [Section 3.4](#).

**Less than 1% of the plutonium that passes through the gastro-intestinal tract reaches the blood.**

### 3.3 Respiratory Tract Models

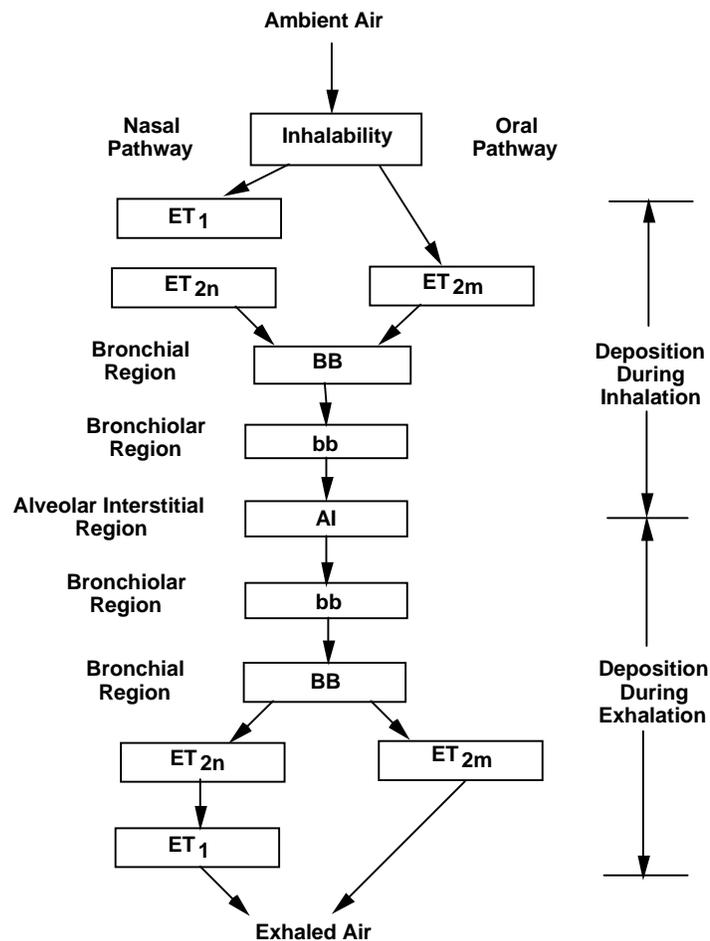
A revised model of the human respiratory tract is presented in ICRP Publication 66 ([ICRP 1994](#)). This model was developed by an international Task Group appointed by ICRP Committee 2, which worked for nearly 10 years to incorporate results of research conducted since publication of the previous model in 1966. As might be expected, the revised model is more detailed and reflects increased knowledge of more physical and biological processes than were considered previously. The following discussion summarizes essential features of the models of deposition and clearance of inhaled particles containing plutonium.

The respiratory tract is divided into several regions in which inhaled particles deposit. In each region, clearance processes act to remove the deposited particles. These regions (and divisions of them) have been given abbreviations, shown in parentheses in the following discussion. Two major regions are distinguished: the extrathoracic (ET) and the thoracic (TH). The extrathoracic region consists of the anterior nose (ET<sub>1</sub>) as well as the posterior nasal passages, larynx, pharynx, and mouth (ET<sub>2</sub>). The thoracic region consists of the bronchial region (BB), the bronchiolar region (bb), and the alveolar interstitial (AI) region. Distinction among these regions is based on the size of the airways, which divide repeatedly to form sequentially smaller passages. Steps in the sequence of subdivision are referred to as “generation *k*” in which *k* reflects the number of prior subdivisions. The bronchial region includes the trachea (the primary inlet passage, generation 0), the two main bronchi (generation 1), and the smaller bronchi of airway generations 2 through 8. The bronchiolar region (airway generations 9–15) consists of bronchioles and terminal bronchioles. The alveolar interstitial region (airway generations 16 and beyond) consists of the respiratory bronchioles, alveolar ducts and sacs with their alveoli, and the interstitial connective tissue. Lymphatic tissue is present in all of these regions. Fluids drain into lymph nodes from the extrathoracic region (LN<sub>ET</sub>). The entire thoracic region is drained by lymph nodes (LN<sub>TH</sub>) located in the bronchial region.

[Section 3.3.1](#) provides more information about particle deposition in the respiratory tract. [Section 3.3.2](#) deals with clearance of the deposited material.

### 3.3.1 Deposition

The revised model ([ICRP 1994](#)) considers the deposition of inhaled particles in the respiratory tract during both inhalation and exhalation of contaminated air. Figure 3-1 shows the air flow path and the opportunities for deposition in each of the compartments. The first box labeled inhalability reflects the availability of airborne particles for inspiration. Inhalability generally decreases with increasing particle size, but under high wind speed conditions it may be enhanced for larger particles. As shown in the figure, the model considers differences when air is inspired and exhaled through the mouth (subscript *m*) compared to the more common use of the nasal passages (subscript *n*). Using the mouth and nose for breathing (called oronasal breathing) is habitual for some individuals. At high levels of exertion nearly everyone uses both nose and mouth for air intake. Both of these features represent additions to the previous lung model.



**Figure 3-1.** Schematic diagram of air flow path and sites of particle deposition in regions of the lung during inhalation and exhalation ([ICRP 1994](#), Figure 8).

Another feature of the new deposition model is consideration of both diffusion of particles and their aerodynamic characteristics. Particle diffusion is the dominant factor in deposition of particles smaller than 0.1  $\mu\text{m}$  in diameter. Diffusion also affects deposition of particles with diameters in the range 0.1–1  $\mu\text{m}$ . Deposition of particles in that size range is determined by a combination of diffusion and aerodynamic parameters. The behavior of particles larger than 1  $\mu\text{m}$  is controlled by their aerodynamic diameter. The new model is better for estimating deposition of particles with diameters in the range 0.001 to 1  $\mu\text{m}$ .

**Deposition of very small particles is controlled by diffusion.**

As shown in [Figure 3-1](#), the respiratory tract can be viewed as a sequence of tissue layers in which particles are deposited as the air is inhaled and then exhaled. Some of the particles are removed as the air passes through each region. The fractional deposition in a particular region applies to the airborne particles reaching that region during either inhalation or exhalation of air.

Deposition in each region of the respiratory tract is predicted using a set of algebraic equations developed to fit experimental data for the extrathoracic region or to fit the predictions of a sophisticated theoretical model of deposition in the thoracic region. In the latter case, the predictions have been compared with limited experimental data and the comparisons have been used to estimate uncertainty bounds for the estimates of fractional deposition. In the revised model ([ICRP 1994](#)), equations used to compute the fractional deposition ( $\eta$ ) for a region have the following general form:

$$\eta = 1 - e^{-caR^p} \quad (3-1)$$

There are separate mathematical expressions for fractional deposition due to aerodynamic and thermodynamic deposition processes in each region and a different set of parameters  $a$ ,  $R$ , and  $p$  for each equation. Values of  $p$  are numerical constants derived from fitting to the experimental data, and values of  $a$  are either numerical constants or a combination of constants and scaling or correction factors. Values of the parameter  $R$  for each region are functions of the particle's aerodynamic diameter or its thermodynamic diameter. The uncertainty in the fractional deposition is incorporated using the parameter  $c$ , which has a lognormal distribution with a median value of 1 and a GSD that depends upon the region of the respiratory tract and the deposition process (aerodynamic or thermodynamic). The best-fit values for  $a$ ,  $R$ , and  $p$  as well as the GSD of the distribution of values of  $c$  have been tabulated by the Task Group ([ICRP 1994](#)) for each region and deposition process.

Two particle diameters are used to characterize properties of aerosols of interest for human inhalation exposure. The motion of larger particles is controlled by inertial and gravitational forces. For those, specification of the aerodynamic diameter relates the properties affecting motion through the air of particles of various shapes and densities to those of a spherical particle of unit density ( $1 \text{ g cm}^{-3}$ ). The aerodynamic diameter ( $d_{ae}$ ) is defined by

$$d_{ae} = d_e \sqrt{\frac{\rho C(d_e)}{\chi \rho_0 C(d_{ae})}} \quad (3-2)$$

where

- $d_e$  = volume equivalent diameter; that is, the diameter of a spherical particle whose volume is the same as the volume of the particle of interest
- $\rho$  = density ( $\text{g cm}^{-3}$ ) of the particle of interest
- $C(d)$  = Cunningham slip correction factor for a particle of diameter  $d$
- $\chi$  = shape factor for the particle, which is greater than 1 if it is not spherical
- $\rho_0$  = density ( $1 \text{ g cm}^{-3}$ ) of the reference particle.

For particles smaller than about  $0.1 \mu\text{m}$ , diffusion is the most important process and the diffusion coefficient is related to the absolute temperature. That is the reason for reference to the “thermodynamic” diameter ( $d_{th}$ ), which is defined by

$$d_{th} = d_e = \frac{kTC(d_e)}{3\pi\mu D} \quad (3-3)$$

where

- $k$  = Boltzmann’s constant,  $1.38 \times 10^{-16} \text{ erg K}^{-1}$
- $T$  = absolute temperature (K)
- $\mu$  = dynamic viscosity of air ( $\text{dyne s cm}^{-2}$ )
- $D$  = diffusion coefficient for the particle ( $\text{cm}^2 \text{ s}^{-1}$ ).

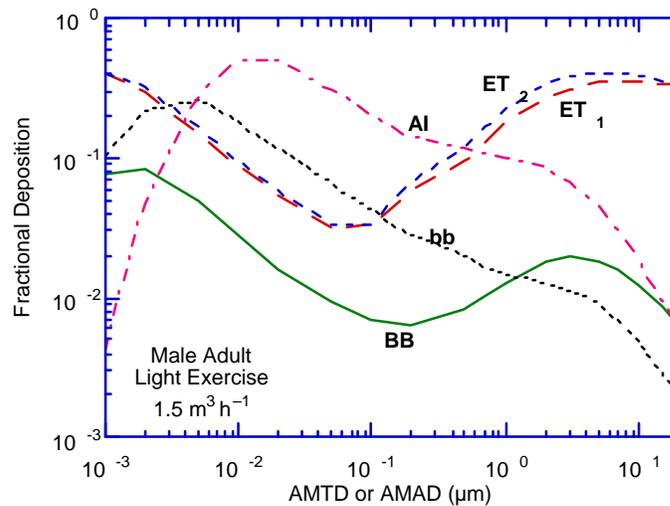
The thermodynamic diameter is related to the aerodynamic diameter by

$$d_{th} = d_{ae} \sqrt{\frac{\chi\rho_0 C(d_{ae})}{\rho C(d_{th})}} \quad (3-4)$$

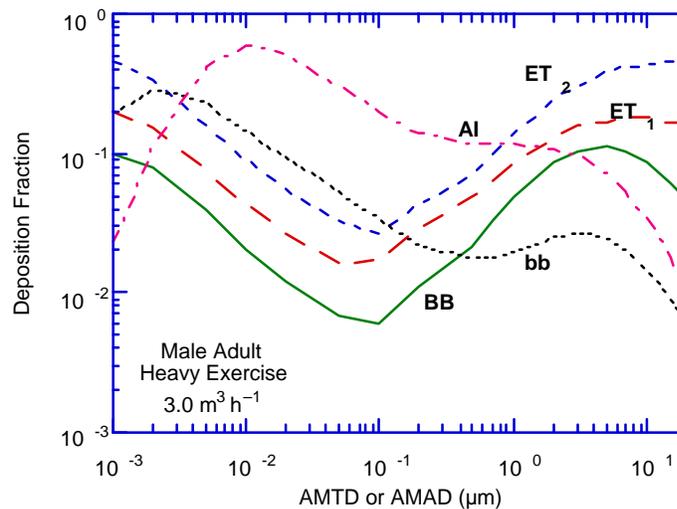
Aerosols generally consist of many particles, whose diameters are not all the same. The distribution of diameters is frequently lognormal and it is common to describe an aerosol using the median diameter and the geometric standard deviation of the distribution of diameters. Half of the aerosol particles have diameters larger than the median value and half the diameters are smaller than that value. The range of particle diameters is described by the GSD of the particle size distribution, which is typically between 2 and 3. For radioactive aerosols, the activity median aerodynamic diameter (AMAD) and the activity median thermodynamic diameter (AMTD) are used.

[Figure 3-2](#) shows results of deposition fraction calculations for a range of particle sizes and two breathing rates that are relevant to this assessment. These plots have been constructed from results tabulated in Appendix F of ICRP Publication 66 ([ICRP 1994](#)).

(a)



(b)



**Figure 3-2.** Deposition fractions for inhalation during (a) light exercise and (b) heavy exercise for an adult male. The shaded regions indicate particle sizes of interest for exposures around Rocky Flats.

The shaded region of [Figure 3-2](#) indicates the range of median particle sizes of interest around Rocky Flats (see [Section 2.4](#)). The two parts of the figure show differences in deposition as a function of the level of exertion. During light exercise, deposition in the two extrathoracic regions ( $ET_1$  and  $ET_2$ ) generally increases with median diameter while deposition in the deeper sections of the respiratory tract ( $bb$  and  $AI$ ) declines with increasing median diameter in the region of interest. During heavy exercise, there is less deposition in the  $ET$  regions, deposition in the bronchial ( $BB$ ) region is substantially greater, and there is some increase in deposition in the bronchiolar ( $bb$ ) and alveolar-interstitial ( $AI$ ) regions.

[Figure 3-2](#) also shows the decline of deposition of particles in the thoracic subregions for median diameters  $>5 \mu\text{m}$ . The deposition that does occur is due to the small particles in the

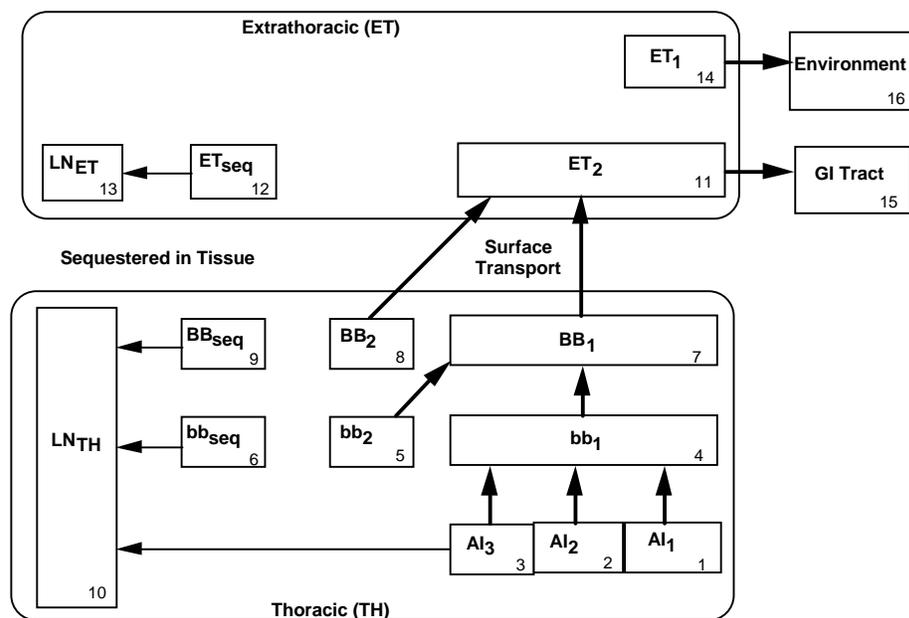
distribution. Particles with  $d_{ae} > 10 \mu\text{m}$  do not reach the bb or AI regions. Particles with  $d_{ae} > 15 \mu\text{m}$  do not even penetrate as far as the bronchial region (ICRP 1994).

### 3.3.2 Clearance

There are two main processes for clearance of particles deposited in the respiratory tract. The first is physical movement of particles to lymph nodes, the GI tract, or the environment (for example, by nose blowing). The second main process is absorption of material into the blood.

The clearance processes are assumed to be competitive; each process acts to remove the material remaining in a compartment at any time. The overall clearance rate from a compartment is the sum of the clearance rates for each process. For mathematical convenience, time-dependent clearance rates for particular regions are approximated by dividing the regions into compartments for which the clearance rates are considered constant. The overall clearance from the region changes with time.

Figure 3-3 shows the compartmental nature of the physical clearance model for each region of the respiratory tract. Arrows indicate clearance of particles that have been deposited in compartments numbered 1–9, 11, 12, and 14. The bolder arrows on the right side of the diagram indicate surface transport via the mucociliary system and the subsequent entry of the particles into the GI tract as a result of swallowing. The inclusion of bronchial region compartments  $BB_2$  and  $bb_2$  in the revised model reflects recent human experimental data that show part of the deposits are cleared more slowly. Similarly, there is evidence that small fractions of the deposited particles are retained in the airway walls; this has been reflected by adding a compartment in each region ( $bb_{seq}$ ,  $BB_{seq}$ , and  $ET_{seq}$ ) to the model to reflect sequestration of material in tissue.



**Figure 3-3.** Compartment model for particle transport in the respiratory tract. The numbers refer to the compartments of this model (from ICRP 1994).

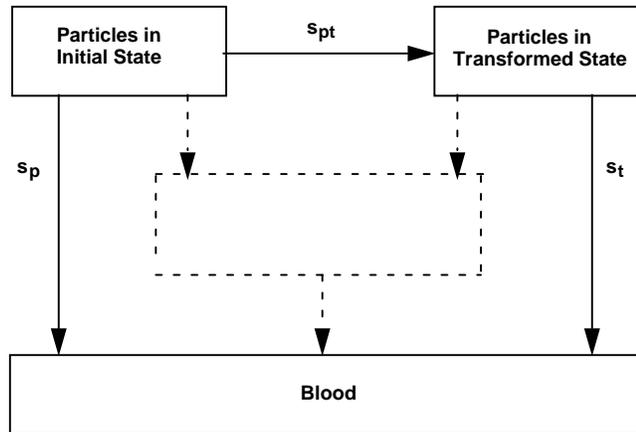
The approximate particle clearance half-time for a process ( $\tau$ , d) can be estimated from the reference clearance rate constant ( $\lambda$ ,  $d^{-1}$ ) using the simple relationship between them ( $\tau = 0.693 \div \lambda$ ). Clearance half-times are about 35, 700, and 7000 days, respectively, for the three deep lung compartments AI<sub>1</sub>, AI<sub>2</sub>, and AI<sub>3</sub>. Half-times for the slowly cleared (23 days) and sequestered deposits (70 days) are estimated to be the same for both the bronchiolar and bronchial regions. Mucociliary clearance is estimated to be more rapid in the upper regions, with approximate half-times of 8.3 hours, 1.7 hours, and 0.17 hour for the bb<sub>1</sub>, BB<sub>1</sub>, and ET<sub>2</sub> compartments, respectively.

In addition to the processes that remove particles from the compartments, processes that lead to absorption of radionuclides into the blood are assumed to occur simultaneously in all compartments except the anterior nasal passage (ET<sub>1</sub>). Both an initial rapid and subsequently slower absorption into blood are considered for three categories of absorption behavior. The three absorption categories are called F (fast), M (moderate), and S (slow) to indicate the general rate of absorption. [Figure 3-4](#) shows the model for absorption to blood. The solid lines and arrows indicate the model as implemented (ICRP 1994). The dashed lines indicate another potential compartment and the associated transport rates included in the general form of the model. The potential compartment was provided for modeling radionuclides whose absorption behavior has been documented adequately to justify added detail.

**Table 3-1. Reference Values of Particle Deposition Fractions and Clearance Rates for Respiratory Tract Compartments**

Compartment	Deposition fraction <sup>a</sup>	Clearance pathway	Clearance rate ( $d^{-1}$ )
AI <sub>1</sub>	0.3	M <sub>1,4</sub>	0.02
AI <sub>2</sub>	0.6	M <sub>2,4</sub>	0.001
AI <sub>3</sub>	0.1	M <sub>3,4</sub> M <sub>3,10</sub>	0.0001 0.00002
bb <sub>1</sub>	0.993– $f_s$	M <sub>4,7</sub>	2
bb <sub>2</sub>	$f_s$	M <sub>5,7</sub>	0.03
Bb <sub>seq</sub>	0.007	M <sub>6,10</sub>	0.01
BB <sub>1</sub>	0.993– $f_s$	M <sub>7,11</sub>	10
BB <sub>2</sub>	$f_s$	M <sub>8,11</sub>	0.03
Bb <sub>seq</sub>	0.007	M <sub>9,10</sub>	0.01
ET <sub>2</sub>	0.9995	M <sub>11,15</sub>	100
Et <sub>seq</sub>	0.0005	M <sub>12,13</sub>	0.001
ET <sub>1</sub>	All	M <sub>14,16</sub>	1

<sup>a</sup>  $f_s$  = fraction of the material that is slowly cleared from the bronchial and bronchiolar regions.



**Figure 3-4.** Compartment model for time-dependent absorption to blood. The dashed arrows and compartment are potentially useful to describe documented behavior but are not implemented in the current model.

The three rate constants ( $d^{-1}$ ) are the dissolution rate for the deposited particles ( $s_p$ ), the transformation rate ( $s_{pt}$ ), and the dissolution rate for transformed particles ( $s_t$ ). [Table 3-2](#) gives the default parameter values for the three rate constants for each of the absorption categories (F, M, and S). As noted earlier, absorption operates in competition with the particle removal mechanisms in each of the compartments 1–14 in [Figure 3-3](#). Both the initial state and transformed state compartments are subject to the particle removal processes.

**Table 3-2. Default Absorption Parameters for Absorption Types F, M, and S**

Model parameters	Type F (fast) <sup>a</sup>	Type M (moderate) <sup>b</sup>	Type S (slow) <sup>c</sup>
Initial dissolution rate, $s_p$ ( $d^{-1}$ )	100	10	0.1
Transformation rate, $s_{pt}$ ( $d^{-1}$ )	0	90	100
Final dissolution rate, $s_t$ ( $d^{-1}$ )	NA	0.005	0.0001

<sup>a</sup> Materials that are readily absorbed into the blood.

<sup>b</sup> Materials with intermediate rates of absorption; the rapidly absorbed fraction is ~10% and the slow clearance half-time is ~100 d.

<sup>c</sup> Relatively insoluble materials; only about 0.1% is absorbed rapidly and the slow clearance half-time is ~7000 d.

Absorption of inhaled plutonium into the bloodstream leads to deposition of plutonium in other internal organs, mainly liver and bone. For that reason, it is important to examine the amounts of inhaled plutonium that reach the blood for various exposure situations. [Table 3-3](#) contains cumulative fractions of inhaled plutonium absorbed into blood for particle sizes of interest in this study and for absorption Types M and S to which plutonium compounds belong. The particle sizes of greatest interest are in the center of the table, between 0.3 and 5  $\mu\text{m}$ . Plutonium oxide is a Type S compound; routine and fire releases would be expected to be of this type. It is uncertain which of the two absorption types is most appropriate for releases from the

903 Area, and it can be seen from [Table 3-3](#) that this uncertainty is more important than any uncertainty in particle size between 1 and 10  $\mu\text{m}$ .

**Table 3-3. Cumulative Absorption to Blood of Plutonium in Particles of Differing Sizes and Absorption Rate**

Particle size AMAD ( $\mu\text{m}$ )	Cumulative absorption to blood	
	Type M	Type S
0.1	0.2	0.04
0.3	0.1	0.02
1	0.09	0.01
5	0.07	0.007
10	0.04	0.004

### 3.3.3 Modifying Factors

A number of factors that affect clearance of material from the respiratory tract have been investigated, including age, various diseases, chemicals, and cigarette smoking. Cigarette smoking is of particular interest because it is a known cause of lung cancer, which is one of the health effects being examined for plutonium. Smoking also reduces the clearance rate of material from the respiratory tract. In general, a slower clearance rate for a compartment leads to a longer residence time and, therefore, to a higher tissue dose.

Table 3-4 contains modifying factors, currently recommended by [ICRP](#) (1994), that affect the clearance of particles from the respiratory tracts of smokers. The modifying factor is used to obtain the parameter value appropriate for smokers. For example, the particle clearance rate  $m_{7,11}$  for smokers would be  $0.5 \times 10 \text{ d}^{-1}$  ([Table 3-1](#)) or  $5 \text{ d}^{-1}$ . In general, the increases in tissue dose attributable to reduced clearance rates are much less important than the substantially increased risk of lung cancer for smokers (see [Chapter 7](#)).

**Table 3-4. Modifying Factors for Clearance Parameters Recommended for Smokers**

Clearance pathway	Clearance rate constant <sup>a</sup>	Modifying factor for smokers
BB <sub>1</sub> to ET <sub>2</sub>	$m_{7,11}$	0.5
bb <sub>1</sub> to BB <sub>1</sub>	$m_{4,7}$	1 <sup>b</sup>
AI <sub>2</sub> to bb <sub>1</sub>	$m_{2,4}$	0.7
AI <sub>3</sub> to bb <sub>1</sub>	$m_{3,4}$	0.7
AI <sub>1</sub>	Fraction to compartments	0.3 <sup>c</sup>

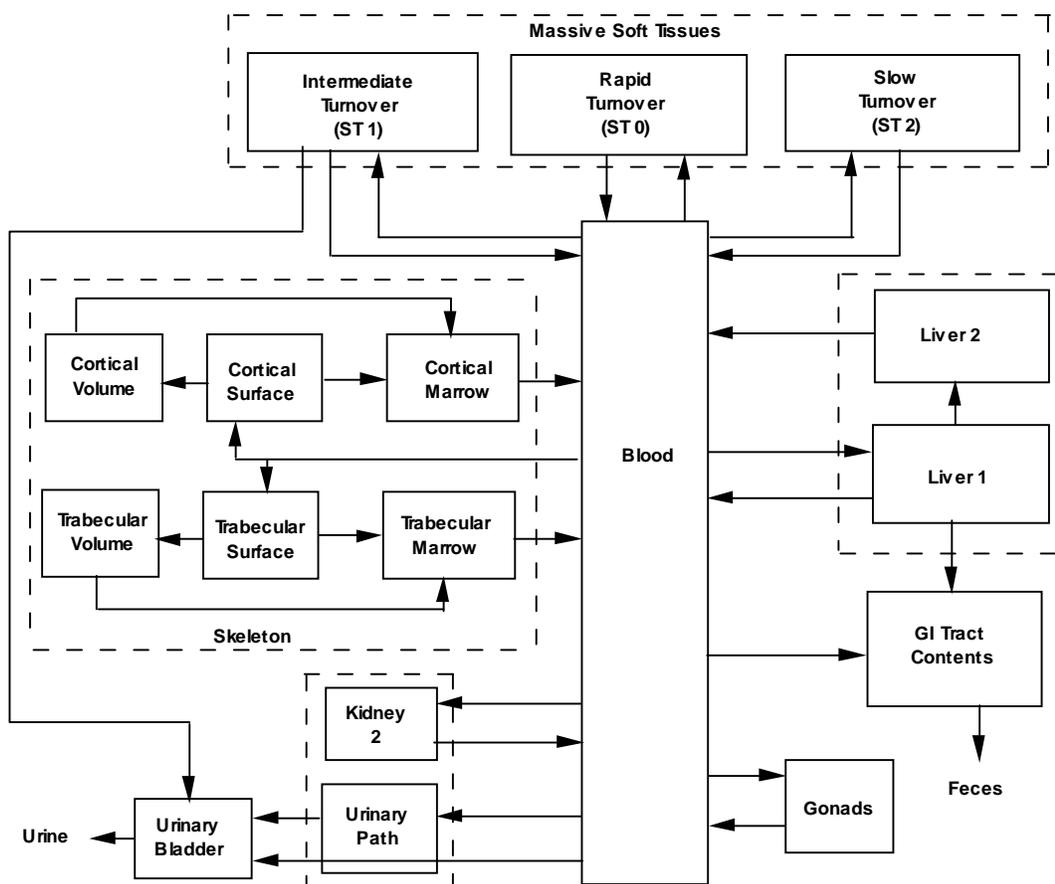
<sup>a</sup> The numbers refer to the compartment model of [Figure 3-4](#).

<sup>b</sup> Recommended values for smokers and nonsmokers are equal.

<sup>c</sup> The fraction assigned to this compartment would be 0.09 instead of the value of 0.3 from [Table 3-2](#); fractions in the slower clearing compartments AI<sub>2</sub> and AI<sub>3</sub> would increase proportionately to 0.78 and 0.13.

### 3.4 Biokinetic Models for Other Tissues

Plutonium cleared from the respiratory tract may reach the blood directly from the locations of deposition, after transfer to the lymph nodes, or from the GI tract. Figure 3-5 shows the model that applies to plutonium that reaches the blood. It does not show the connections to the lung and GI tract. The blood is treated as a well-mixed pool that serves as a conduit for plutonium distribution to organs and tissues. Movement of plutonium between compartments is treated as a combination of first order rate processes; that is, the fractional removal of material per unit time from any compartment is taken to be a constant. In Figure 3-5, transfer processes are indicated by arrows that show the direction of transfer.



**Figure 3-5.** Details of the ICRP biokinetic model for plutonium that reaches the blood following inhalation or ingestion (ICRP 1993a).

The rapid turnover soft tissue compartment (ST 0), which includes extracellular fluids, rapidly exchanges material with the blood compartment. Together these two compartments provide a reasonable representation of the short-term kinetics observed in humans and other primates receiving plutonium injections. The model also contains two other soft tissue compartments, with intermediate and slow turnover rates (ST 1 and ST 2, respectively). These

compartments represent muscle, skin, fat, and other soft tissues that are not modeled explicitly. The skeleton is subdivided into the cortical bone and trabecular bone subcompartments. Cortical bone is compact and highly mineralized. Trabecular bone is spongy and contains marrow. The liver and kidney are also subdivided into regions with different retention half-times.

The model shown in [Figure 3-5](#) is the result of a long-term effort to address questions about radiation dosimetry for plutonium and other actinides in humans. The actinide assessments are chronicled in a series of reports, the first of which was ICRP Publication 19 ([ICRP 1972](#)). The next detailed review was published as ICRP Publication 48 ([ICRP 1986](#)). The model has been revised further and age-dependent parameters have been incorporated ([ICRP 1989a](#), [1993a](#)).

Although the biokinetic model for plutonium is mathematically defined in terms of a set of rate constants, it is perhaps easier to think of the process in terms of deposition of plutonium in and its clearance from various tissues. The earlier, simpler biokinetic models were developed using these concepts. Table 3-5 contains the fractions of plutonium leaving the circulation that are received by the several tissue compartments ([ICRP 1993a](#)). Eighty percent of the plutonium goes to either the skeleton or the liver; in adults the skeleton:liver proportion is 5:3. The skeletal fraction is apportioned between the two types of bone. The liver fraction all goes into liver 1, which is the liver compartment with relatively rapid clearance.

**Table 3-5. Fractions of the Plutonium Reaching the Blood That Are Deposited in Adult Tissues**

Tissue compartment	Fraction
Cortical bone surface	0.3
Trabecular bone surface	0.2
Liver 1	0.3
Gonads <sup>a</sup>	
Ovaries	0.00011
Testes	0.00035
Kidney, urinary path	0.01
Kidney 2	0.005
Urinary bladder	0.02
Soft tissue, slow turnover (ST 2)	0.02
Soft tissue, intermediate (ST 1)	0.12 <sup>b</sup>

<sup>a</sup> Based upon a deposition fraction of 0.001% g<sup>-1</sup> of gonadal tissue.

<sup>b</sup> Computed by difference after considering all other compartments including ST 0.

Gonadal deposition is based on tissue mass, with a correspondingly greater deposition in the testes ([ICRP 1986](#), [Thomas et al. 1989](#)). Approximately 1.5% of the plutonium is deposited in kidney tissues, with 0.5% deposited in kidney tissues (in the compartment called kidney 2) and 1% deposited along the urinary excretion pathway. Another 2% is transferred to the urinary bladder directly. Differences in clearance from these tissues are discussed below. This approach is in reasonable agreement with urinary excretion data following either injection or occupational exposure. The estimated deposition fraction for material retained for a long time in soft tissue (ST 2) agrees with autopsy data from persons whose exposures occurred many years before

death. The fraction for the intermediate turnover soft tissue compartment (ST 1) is used to account for material not otherwise assigned on the basis of specific information from human or animal studies.

Plutonium is assumed to be removed from compartments according to first order kinetics. [Table 3-6](#) contains the removal rate constant ( $\lambda$ ,  $d^{-1}$ ) for each process removing material from deposition locations indicated in [Figure 3-5](#) (ICRP 1993a). [Table 3-6](#) includes the rate constants for transfers among bone compartments. For convenience, the corresponding clearance half-time ( $\tau$ , d) is shown ( $\tau = 0.693 \div \lambda$ ). When two processes with rate constants  $\lambda_1$  and  $\lambda_2$  operate on the same compartment, the effective clearance rate constant is  $\lambda_e = \lambda_1 + \lambda_2$ . In these cases, the effective half-time ( $\tau_e = 0.693 \div \lambda_e$ ) is given in the table. Values of the clearance and effective clearance half-times have been rounded to two significant figures. Because there is transfer *to* and *from* many of the compartments, the tabulated half-time is not the one that would be observed if one could obtain a time sequence of measurements of the amount of plutonium in a particular compartment. Instead, the value in the table reflects the underlying biological removal rate for that compartment.

Rates of removal of plutonium from bone reflect the rates of bone formation and remodeling (ICRP 1989a, 1993a), which are relatively slow processes. Clearance half-times for bone compartments are shown in the upper portion of Table 3-6. The combined removal of activity to the cortical bone volume and marrow yields an effective half-time for plutonium deposited on

**Table 3-6. Clearance Rate Constants and Half-times for Plutonium in Adults**

Plutonium clearance route		Clearance rate constant ( $\lambda$ , $d^{-1}$ )	Clearance half-time ( $\tau$ , d)
From	To		
Cortical bone surface	Cortical bone volume	0.0000411	<sup>a</sup>
Cortical bone surface	Cortical bone marrow	0.0000821	5,600 <sup>a</sup>
Cortical bone volume	Cortical bone marrow	0.0000821	8,400
Trabec. bone surface	Trabec. bone volume	0.000247	<sup>a</sup>
Trabec. bone surface	Trabec. bone marrow	0.000493	940 <sup>a</sup>
Trabec. bone volume	Trabec. bone marrow	0.000493	1,400
Either bone marrow	Blood	0.0076	91
Liver 1	Liver 2	0.00177	<sup>a</sup>
Liver 1	Small intestine	0.000133	360 <sup>a</sup>
Liver 2	Blood	0.000211	3,300
Soft tissue 0	Blood	0.693	1
Soft tissue 1	Blood	0.000475	<sup>a</sup>
Soft tissue 1	Urinary bladder	0.000475	730 <sup>a</sup>
Soft tissue 2	Blood	0.000019	36,000
Ovaries or testes	Blood	0.00019	3,600
Kidney, urinary path	Urinary bladder	0.01386	50
Kidney 2	Blood	0.00139	500

<sup>a</sup> When two processes clear material from the same compartment, an effective clearance half-time has been computed. For example, the clearance rates from cortical bone surfaces combine to give  $\lambda_e = 0.0000411 + 0.0000821 = 0.0001232 d^{-1}$ ; thus, the effective clearance half-time is  $\tau_e = 0.69315 \div 0.0001232 = 5626$  days (rounded to 5600 days).

cortical bone surfaces of 5600 days (~15 years). Turnover in trabecular bone is faster as indicated by the smaller clearance half-times.

The model for plutonium in liver has been modified to reflect information from human autopsy data on long-term plutonium distribution ([ICRP 1989a](#)). The effective clearance half-time for the compartment called liver 1, associated with hepatocytes, is 1 year. Most of the plutonium goes to liver 2, associated with reticulo-endothelial cells, from which it is cleared with a 9-year half-time.

As noted earlier, there is rapid interchange between ST 0 compartment and the blood. Clearance from the two other soft tissue compartments is slower with half-times of 2 years for ST1 and 100 years for ST 2.

The clearance rate assigned to the gonads is equivalent to a retention half-time of 10 years. The estimated long-term concentration of plutonium in the gonads is roughly constant because of continued uptake from the blood. This concentration is consistent with many of the animal studies; however, studies of primates have indicated that clearance occurs ([ICRP 1986](#)).

The model for retention of plutonium in the kidneys reflects experimental data for plutonium and americium and urinary excretion information for humans and animals. Clearance half-times are 50 and 500 days for the two compartments of deposition. The excretion path from ST 1 was explicitly included to reflect observations of plutonium excretion patterns in exposed humans.

The deposition fractions and clearance half-times for the various compartments are directly relevant to plutonium dosimetry. Together they determine the numbers of radioactive disintegrations that will occur in a particular tissue compartment, a critical factor for evaluating dose to that tissue.

### **3.5 Plutonium Dosimetry**

The following discussion of plutonium dosimetry focuses on the absorbed dose, which reflects the fundamental process of energy deposition in tissue. The risk estimates developed elsewhere in this report are related to the absorbed dose in the principal organs of interest identified in [Chapter 2](#) (lung, liver, and bone). [Section 3.5.1](#) provides definitions of the quantities used to calculate absorbed dose and committed absorbed dose. [Section 3.5.2](#) identifies target tissues in those organs and [Section 3.5.3](#) discusses alpha particle energy absorption in those tissues. Reference dose estimates are given in [Section 3.5.4](#).

#### **3.5.1 Absorbed Dose and Committed Absorbed Dose**

The central physical quantity of interest in the dosimetry of ionizing radiations is called the absorbed dose. Simply stated, it is the amount of energy imparted to a unit mass of tissue by ionizing radiations that pass through the tissue. The historic unit of absorbed dose is the rad, which corresponds to an energy deposition of 100 ergs per gram of tissue. The SI unit is the gray (Gy), which corresponds to deposition of 1 joule of energy per kilogram of tissue; 1 Gy equals 100 rad.

For some radionuclides it is possible to make physical measurements of the radiation emitted from the whole body, or from specific organs, and to use the data to estimate the corresponding absorbed doses to tissues. Plutonium, an alpha-emitting radionuclide, does not emit sufficient penetrating radiation to permit reliable measurements of tissue burdens in living

members of the public. Doses from plutonium taken into the body must be calculated using biokinetic models, described above, and knowledge of the physical quantities that determine the dose.

The absorbed dose from plutonium depends upon a number of quantities. The first of these is the amount of plutonium that is taken into the body and subsequently resides in particular organs or tissues. For radiation dose calculations, the quantity of radioactive material is defined as the number of radioactive transformations per unit time. This quantity is called the activity and the SI unit is the becquerel (Bq), which corresponds to 1 transformation per second. The historic unit of activity is the curie (Ci); 1 Ci =  $3.7 \times 10^{10}$  Bq. The microcurie ( $\mu\text{Ci}$ ), one millionth of a curie or 37,000 Bq, is a more common unit as is the nanocurie (nCi), one billionth of a curie or 37 Bq.

Other physical quantities used to estimate radiation dose are the half-life of the radionuclide, the number and types of radiations emitted when radioactive disintegrations occur, and knowledge of how the energy from the emitted radiation is absorbed in tissue. Information about the half-lives of radionuclides and the radiations that they emit has been compiled ([Lederer and Shirley](#) 1978; [ICRP](#) 1983). The half-lives of the principal isotopes of concern,  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ , are very long: 24,065 and 6537 years, respectively. The most important emissions from these radionuclides are alpha particles, with energies between 5.1 and 5.2 million electron volts (MeV). Although other radiations are emitted when an atom of  $^{239}\text{Pu}$  or  $^{240}\text{Pu}$  disintegrates, the alpha particles carry more than 98% of the emitted energy. Thus, they are the primary concern for dosimetry. Nearly all of the remaining energy is carried by the recoil energy of the atom undergoing the transformation. The total energy emitted by  $^{239}\text{Pu}$  or  $^{240}\text{Pu}$  is between 5.24 and 5.26 MeV per transformation ([ICRP](#) 1983).

**The absorbed dose in a tissue is the amount of energy deposited divided by the mass of the tissue.**

Alpha particles interact strongly with the atoms in the medium through which they pass, and they deposit their energy in a relatively short distance compared with other radiations having similar energies. In the liver (for example), an alpha particle from  $^{239}\text{Pu}$  gives up all its energy along a path length of  $\sim 46 \mu\text{m}$ , its range in soft tissue. The average LET, the amount of energy transferred per unit path length, for a 5.15-MeV alpha particle is about  $110 \text{ keV } \mu\text{m}^{-1}$ . This may be compared with LETs of  $\leq 3.5 \text{ keV } \mu\text{m}^{-1}$  for gamma radiation. The comparison shows the quantitative difference in energy absorption between high- and low-LET radiations. The fraction of the alpha particle energy that is absorbed by a particular target tissue depends upon the location of the alpha particle emission and on tissue dimensions and densities. In parts of the lung, alpha particles can travel farther than in solid tissue because of the presence of air spaces.

In most cases the tissue containing the plutonium, called the source tissue, is the same as the target tissue, the tissue whose dose we wish to compute. This is the case in the example of dose to the ovaries, which is discussed below to illustrate a simple dose calculation. However, in the calculation of doses to the respiratory tract and to the bone, the target tissues are very specific layers of cells that are in some cases separated from the sites of plutonium deposition. For those tissues, some of the plutonium alpha particle energy emitted will be absorbed in the intervening tissue layers.

The dose estimation procedure for plutonium combines the quantities that have been discussed above. Consider the estimation of the average absorbed dose ( $D$ ) to a tissue that contains a uniform distribution of  $^{239}\text{Pu}$  throughout its mass ( $m$ ). The absorbed dose is given by

$$D = \frac{1.6 \times 10^{-13} U \sum_i Y_i E_i A F_i}{m} \quad (3-5)$$

where

$1.6 \times 10^{-13}$	=	(joule MeV <sup>-1</sup> ) energy conversion constant
$U$	=	the total number of transformations of <sup>239</sup> Pu that occur in the tissue
$Y_i$	=	the fraction of transformations resulting in emission of radiation of type $i$
$E_i$	=	the energy (MeV) of radiation $i$ that is emitted
$A F_i$	=	the fraction of the energy of type $i$ that is absorbed in the target tissue
$m$	=	the mass (kg) of the target tissue.

Examining the dimensions of the quantities in [Equation \(3-3\)](#) shows that the dose has units of joules per kilogram (J kg<sup>-1</sup>) or gray.

In this equation, the summation (indicated by  $\Sigma$ ) is over all three terms for each type of radiation emitted. When the <sup>239</sup>Pu is uniformly distributed in the target tissue, the alpha particle and nucleus recoil energies are completely absorbed by the target tissue. Thus, the summation gives the 5.24–5.26 MeV per transformation cited above. When a thin target tissue is located some distance from the site of deposition, the absorbed fraction is less than one and its calculation must address the relative positions of the sources and targets and the type and amount of intervening tissue.

The dose from long-lived radionuclides, like <sup>239</sup>Pu and <sup>240</sup>Pu, is not delivered instantaneously. The plutonium is retained for long times in lung, liver, and bone and the doses to those tissues are received over a period of years. One way to address this is to compute the *committed* dose for a specified time period. This is the total dose that will be received during that time due to a particular intake of radioactivity. The calculation of committed dose assumes that radionuclide retention is correctly predicted by the biokinetic model and that the individual lives for the specified time period.

The total number of nuclear transformations occurring in a tissue is the time-integrated activity of the radionuclide in that tissue. Mathematically, this is given by the equation

$$U = \int q(t) dt \quad (3-6)$$

where  $q(t)$  is the time-dependent activity of the radionuclide in the tissue and the symbol  $\int$  indicates integration over time. The function  $q(t)$  depends upon the biokinetic model. The time limits of the integral can be selected to suit the problem.

To take a simple case, let us assume that the target tissue for our calculation is the ovaries ( $m = 0.011$  kg). It was noted above that the many experimental studies in non-primates indicate, and the current metabolic model predicts, a nearly constant concentration in that tissue following the initial uptake. If we take  $q(t)$  to be a constant, say 0.037 Bq (1 pCi), then  $U$  is simply the product of the activity and the exposure time. To calculate the 50-year committed dose ( $D_{50}$ ), for example, the total number of disintegrations is  $U = 0.037 \text{ Bq} \times 50 \text{ y} \times 3.156 \times 10^7 \text{ s y}^{-1} = 5.84 \times 10^7 \text{ Bq s}$  or  $5.84 \times 10^7$  transformations. Using the dose equation given above, we find for this simple example that

$$D_{50} = \frac{(1.6 \times 10^{-13} \text{ J MeV}^{-1}) \times (5.84 \times 10^7 \text{ trans}) \times (5.25 \text{ MeV trans}^{-1})}{0.011 \text{ kg}}$$

$$= 0.0045 \text{ J kg}^{-1} = 0.0045 \text{ Gy} = 0.45 \text{ rad} \quad (3-7)$$

In other cases the amount of activity in a tissue will vary with time. In simple cases, this variation can be expressed as

$$q(t) = q_0 e^{-\lambda t} \quad (3-8)$$

where  $q_0$  is the initial activity (Bq) deposited in the tissue and  $\lambda$  ( $\text{s}^{-1}$ ) is the clearance rate constant. This type of expression would apply, for example, to determine the number of transformations for plutonium deposited in ST 1, ST 2, the kidney compartments, and liver 1. For sequential transfers, as from liver 1 to liver 2, the expression for  $q(t)$  for liver 2 is more complex. The integral in the equation for  $U$  is correspondingly more complicated, but it can still be performed in a straightforward manner. The equations for the bone compartments are similarly complex but equally tractable.

For  $^{239}\text{Pu}$  and  $^{240}\text{Pu}$ , the radioactive decay rate constants ( $7.9 \times 10^{-8} \text{ d}^{-1}$  and  $2.9 \times 10^{-7} \text{ d}^{-1}$ , respectively) are so small that they can be ignored when estimating losses of activity from the various tissue compartments. Note that the smallest biological clearance rate constant in either [Table 3-2](#) or [Table 3-6](#) is  $1.9 \times 10^{-5} \text{ d}^{-1}$ , more than 100 times larger than the decay rate constant for  $^{240}\text{Pu}$ .

In summary, the absorbed dose and committed absorbed dose depend upon the number of transformations that occur in or near the exposed tissue and upon the amount of energy absorbed in that tissue per transformation. The plutonium activity that reaches a tissue and its retention by the tissue determine the number of transformations that will occur in the tissue. Both the initial deposition and the retention are estimated using models of deposition and clearance for the respiratory tract and for other organs and tissues that receive plutonium from the blood.

### 3.5.2 Primary Target Tissues

In the simple example given above, the target tissue was taken to be the entire mass of the organ. The dose is frequently averaged over the whole organ or tissue when there is insufficient information about either the cells at risk or the relative positions of the source tissue and the target cells. This is currently the situation for the liver, one of the principal tissues of concern following intake of plutonium, and most other tissues in [Table 3-5](#). As more information becomes available, the dosimetric models for more tissues may address specific cellular, or even subcellular, targets.

For other tissues of concern in this work, the sensitive cells and the locations of the contamination are sufficiently well known to estimate doses to specific cells at risk. This is the case for both bone, as suggested by [Figure 3-5](#), and for the respiratory tract, [Figure 3-3](#). As discussed elsewhere in this report, the dose to endosteal cells (which line the surfaces of marrow cavities in bones) is considered most important for inducing bone cancer. ICRP Publication 30 adopted a modified dosimetry model to assess doses to the thin layer of cells on bone surfaces from internally deposited radionuclides like plutonium ([ICRP 1979](#)).

For lung dosimetry, the effort to address doses to specific tissues began with the first detailed lung model (ICRP 1966), but it was only completed recently in ICRP Publication 66 (ICRP 1994). Doses to sensitive cells in the bronchial tree were considered in the evaluations of lung cancer risks from radon and the associated alpha-emitting progeny by both the National Council on Radiation Protection and Measurements (NCRP) and the ICRP (NCRP 1984; ICRP 1987). In the current ICRP model, doses are calculated for target tissues in each of the main compartments in the thoracic region (BB, bb, AI, and LN<sub>TH</sub>; see Figure 3-3). The tissues in the thoracic region constitute what has traditionally been called the lung. For the BB and bb targets, there are multiple sources. The extrathoracic region is now treated as a separate tissue, called the extrathoracic airways, for radiation dosimetry with three target tissue compartments: ET<sub>1</sub>, ET<sub>2</sub>, and LN<sub>ET</sub> (see Figure 3-3).

Assessing doses to multiple components of the lung and the ET airways leads to the question of the importance that should be attached to the component doses. To address this issue, the ICRP developed a set of assigned fractions of the tissue weighting factor. These fractions are used to weight the dose to each region to determine its contribution to the overall tissue dose. If there were unique risk factors that related dose to a particular region to cancer incidence, this approach would not be necessary. However, such risk factors are not available (or even foreseeable) and a composite dose to the lung is necessary for both risk estimation and radiation protection.

Table 3-7 lists the masses of target tissues within the lung, skeleton, and liver for adults. Male and female values for lung tissues differ somewhat and have been averaged. The values for the respiratory tract are averages of the male and female values established for the new model (ICRP 1994). Masses for the skeletal tissues are from ICRP Publication 70 (ICRP 1995a). Table 3-7 also includes the assigned fractions for the thoracic region of the lung. These fractions, which are estimates of the relative importance of the various target tissues, are used to compute the weighted absorbed dose (or weighted committed absorbed dose) to the lung. The number of significant figures shown should not be interpreted to be an indication of radiobiological understanding of the relationship between radiation dose and lung cancer production. For the extrathoracic region, the ICRP assigned a fraction of 1 to ET<sub>2</sub> and assigned fractions of 0.001 to both the anterior nose (ET<sub>1</sub>) and the extrathoracic lymph nodes.

Table 3-8 illustrates the dependence on age of target tissue masses for lung, liver, and skeleton (ICRP 1994, 1995b). For the target tissues in the lung, values for females and males, which differ slightly, have been averaged.

**Table 3-7. Adult Masses of Target Tissues of Primary Interest for Plutonium Intakes and Assigned Fractions for Regions of the Lung**

Organ or tissue	Tissue mass (g)	Assigned fraction <sup>a</sup>
Lung (thoracic regions)		
Bronchial region, secretory cells (BB <sub>sec</sub> )	0.82 <sup>b</sup>	0.1665
Bronchial region, basal cells (BB <sub>bas</sub> )	0.41 <sup>b</sup>	0.1665
Bronchiolar (bb) region	1.9 <sup>b</sup>	0.333
Alveolar-interstitial (AI) region	1,000 <sup>b</sup>	0.333
Thoracic lymphatics (LN <sub>TH</sub> )	13.5 <sup>b</sup>	0.001
Liver	1,800	
Skeleton		
Endosteal cells, cortical bone surfaces	60	
Endosteal cells, trabecular bone surfaces	60	
Active marrow	1,500	
Bone volume (cort.: 4000 g, trab.: 1000 g)	5,000	

<sup>a</sup> These factors are used to weight the doses to individual regions in the calculation of dose to the lung.

<sup>b</sup> Average of female and male values.

**Table 3-8. Target Tissue Masses for Various Ages**

Organ or tissue	Mass (g) of target tissue at specified age				
	1 year	5 years	10 years	15 years	Adult
Lung <sup>a</sup>					
BB <sub>sec</sub>	0.31	0.47	0.62	0.79 <sup>b</sup>	0.82 <sup>b</sup>
BB <sub>sec</sub>	0.16	0.23	0.31	0.395 <sup>b</sup>	0.41 <sup>b</sup>
bb	0.60	0.95	1.3	1.7 <sup>b</sup>	1.9 <sup>b</sup>
AI	150	300	500	830 <sup>b</sup>	1000 <sup>b</sup>
Liver	292	584	887	1400	1800
Skeleton					
Endosteal cells	26	37	68	120	120
Active marrow	150	320	610	1050	1500
Bone volume	499	1094	1980	4030	5000

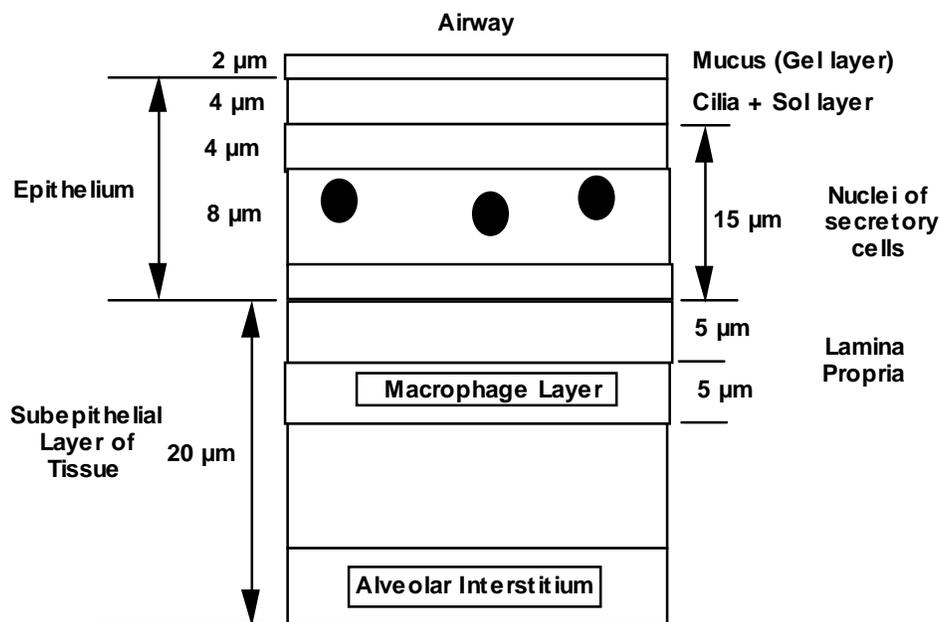
<sup>a</sup> Tissue codes are BB<sub>sec</sub>: secretory cells; BB<sub>bas</sub>: basal cells, bronchial region; bb: bronchiolar region; AI: alveolar interstitial region.

<sup>b</sup> Average of female and male values.

### 3.5.3 Fractions of Alpha Particle Energies Absorbed

The fractions of the emitted alpha particle energy that are absorbed in the several target tissues are discussed in this section. The target tissues in the respiratory tract are discussed first, followed by the absorbed fractions for alpha particles emitted in liver and bone.

The fractions of the emitted alpha particles absorbed in the respiratory tract target tissues have been computed using Monte Carlo techniques (ICRP 1994). The trajectories of many alpha particles emitted in a region of deposition were followed to calculate the fraction of the emitted energy that was deposited in a target tissue. These calculations address the physical arrangement of sources, intervening tissue, and target tissue by simulating the particle trajectories through the tissues. Figure 3-6 provides an example of the type of model used for the calculations for the bb region, which contains secretory cells considered to be radiosensitive target cells. Particles deposited on the interior of the bronchiolar airway or carried by the mucociliary transport mechanism from lower regions would be carried past the cells on the mucous layer. Sequestered particles would be in the macrophage layer and other particles would be located in the alveolar interstitium. Particles in all these locations would irradiate the target secretory cells, and the fractions of the alpha particle energy absorbed by the targets would differ because of differences in the thicknesses of intervening tissues.



**Figure 3-6.** Model of target cells and bronchiolar wall (bb region). Sources of alpha particle emission would be on the mucus layer, bound in the epithelial layer, sequestered in macrophages, or in adjoining alveolar interstitial tissue.

Models similar to that shown in Figure 3-6 were developed for other regions in the respiratory tract and are presented in ICRP Publication 66 (ICRP 1994) in similar dimensional detail. Such models served as the basis for the calculations of absorbed fractions for alpha particles and other radiations. Table 3-9 contains the results of the Monte Carlo calculations for

5.15-MeV alpha particles from [ICRP \(1994\)](#). In situations where the source is farther from the target than the range of the alpha particle in tissue, the absorbed fraction is zero because the alpha particle cannot reach the target cells. The secretory cells are located above the basal cells of the bronchial region and, thus, receive more energy from the sources on the mucociliary escalator and less from those sequestered in the macrophage layer.

For sources within the AI region, the absorbed fraction for alpha particles is taken to be one because the sensitive target cells are assumed to be uniformly distributed within the tissue. The contributions from alpha particles emitted in other regions (bb, BB, and ET) are considered insignificant, which is consistent with the small absorbed fractions for those regions because of sources in the AI region (Table 3-9). The target cells and sources of radiation are both assumed to be uniformly distributed in thoracic lymph nodes. As a result, the absorbed fraction for alpha particles is one for that tissue as well.

**Table 3-9. Absorbed Fractions for 5.15-MeV Alpha Particles in Lung Tissues<sup>a</sup>**

Target tissue	Sources for basal and secretory cell targets in the thoracic region				
	Fast mucus	Slow mucus	Bound	Sequestered	AI region
BB <sub>bas</sub>	0	0.00054	0.219	0.135	0
BB <sub>sec</sub>	0.144	0.192	0.454	0.0515	0
bb	0.233	0.237	0.244	0.111	0.0000706

<sup>a</sup> Results of Monte Carlo calculations from tabulation in Appendix H of ICRP Publication 66 ([ICRP 1994](#)).

As noted above, the dose to the liver is averaged over the entire mass of the organ because target cells that are particularly at risk for cancer induction have not been identified. For that case, as for the AI region of the lung, the absorbed fraction is equal to one.

For radionuclides in bone there are two sensitive tissues: the endosteal cells on both cortical and trabecular bone surfaces and the red bone marrow, which is located in trabecular bone. Generic absorbed fractions for all alpha-emitters were estimated in Part 1 of ICRP Publication 30 ([ICRP 1979](#)) and are presented in [Table 3-10](#). For some fractions, values for the 5.15-MeV plutonium alpha particles have been estimated by interpolating results discussed in ICRP Publication 30 ([ICRP 1979](#)), and [Table 3-10](#) presents these values in parentheses for comparison.

**Table 3-10. Absorbed Fractions for Alpha Particles in Sensitive Tissues in Bone<sup>a</sup>**

Target tissue	Sources distributed in bone volume		Sources on bone surfaces	
	Trabecular	Cortical	Trabecular	Cortical
Endosteal cells	0.025 (0.024) <sup>b</sup>	0.01	0.25 (0.31) <sup>b</sup>	0.25 (0.31) <sup>b</sup>
Red marrow	0.05 (0.05) <sup>b</sup>	0	0.5	0

<sup>a</sup> Generic values for alpha particles from ICRP Publication 30 ([ICRP 1979](#)).

<sup>b</sup> Values in parentheses are interpolated estimates from information in ICRP Publication 30 ([ICRP 1979](#)).

The work of [Smith et al. \(1984\)](#) suggests that the situation is more complex than the one addressed by current models. They note that most osteosarcomas occur in areas that contain red marrow, while tumors are not frequently found in areas containing yellow (fatty) bone marrow.

Their investigation in beagle dogs suggests that higher deposition of plutonium in areas containing red marrow is related to the vascular structure of those locations. They found a distinct difference between plutonium deposition in areas adjacent to red and yellow marrow and that this difference is likely related to vascular structure.

### 3.5.4 Reference Dose Estimates for Primary Targets

[Table 3-11](#) provides estimates of absorbed dose for a reference  $^{239}\text{Pu}$  aerosol, which were made using the new model of the respiratory tract and the current biokinetic model for plutonium (ICRP 1995a). The reference AMAD of  $1\ \mu\text{m}$  lies near the center of the size range of interest ([Figure 3-3](#)). For convenience, these dose coefficients, which apply to adults, are given in SI units (microgray per becquerel inhaled) and historic units (millirad per nanocurie inhaled). All values have been rounded to two significant figures. Absorption type S is appropriate for the plutonium dioxide known to have been released routinely from Rocky Flats and during the fires.

The result for lung in [Table 3-11](#) reflects applying the weighting factors shown in [Table 3-7](#). Within the lung, the highest doses to radiosensitive tissues are received by tissues in the AI region, followed by secretory cells in the BB region, and the secretory cells in the bb region. Unadjusted absorbed doses to those tissues for absorption type S are 6.5, 5.3, and  $2.9\ \mu\text{Gy Bq}^{-1}$  inhaled (24, 19, and 11 mrad  $\text{nCi}^{-1}$  inhaled), respectively. Doses to the basal cells of the bronchial region are about a factor of 10 lower than the average doses to those three tissues and doses to thoracic lymph nodes are higher than the average by about the same factor. The demonstrated absence of lymphatic system tumors in experimental studies of plutonium inhalation (ICRP 1980) is the basis for the small assigned fraction ([Table 3-7](#)).

**Adults receive higher doses from exposure to the same concentration of airborne plutonium than children or infants.**

Table 3-11 also contains dose coefficients for absorption type M. The faster absorption is appropriate for plutonium nitrate and other compounds that are more soluble than plutonium dioxide. Because the 903 Area contamination involved organic compounds and extended environmental exposure, releases from that area may have contained plutonium compounds with greater solubility than the oxide.

**Table 3-11. Absorbed Dose Coefficients for Unit Intakes of Reference  $^{239}\text{Pu}$  Aerosols with AMAD =  $1\ \mu\text{m}$**

Organ or tissue <sup>a</sup>	Absorbed dose coefficients for unit intakes of $^{239}\text{Pu}$ reference aerosol: $1\text{-}\mu\text{m}$ AMAD, GSD = 2.5			
	Absorption type S		Absorption type M	
	$\mu\text{Gy Bq}^{-1}$	mrad $\text{nCi}^{-1}$	$\mu\text{Gy Bq}^{-1}$	mrad $\text{nCi}^{-1}$
Lung	4.4	16	1.6	6.1
Liver	2.0	7.3	16	61
Skeleton				
Bone surface	9.0	33	75	280
Red marrow	0.46	1.7	3.7	14

The values in [Table 3-11](#) are not intended to be definitive for any particular exposure situation, but they do indicate the relative magnitudes of the absorbed doses that may be received by particular tissues following inhalation exposures. For absorption type S, the calculations show that bone surfaces receive the highest doses, followed by lung and liver. Bone surfaces are also estimated to receive the highest doses for absorption type M, followed by liver, red marrow, and lung. The dose coefficients in [Table 3-11](#) are normalized to a unit intake of plutonium by inhalation. An alternative approach is to normalize the dose coefficients to a unit of exposure, represented by the time-integrated air concentration. The time-integrated air concentration is the product of the average air concentration during the period of exposure and the duration of the exposure. (A person breathing an average concentration of  $1 \text{ Bq m}^{-3}$  for 5 hours would be exposed to a time-integrated air concentration of  $5 \text{ Bq h m}^{-3}$ ). The product of the time-integrated air concentration ( $\text{Bq h m}^{-3}$ ) and the breathing rate ( $\text{m}^3 \text{ h}^{-1}$ ) is the intake (Bq). Absorbed dose coefficients per unit exposure [ $\mu\text{Gy} (\text{Bq h m}^{-3})^{-1}$ ] are another useful way to express dosimetry results.

Table 3-12 contains absorbed dose coefficients per unit exposure for five ages derived from [ICRP \(1995b\)](#). Comparing the values indicates that for exposures of equal duration to the same air concentration, adults will receive higher doses than younger people. The biggest difference between adults and infants is for dose to bone surfaces. This is due to the much greater growth rate of bones in children. Ratios of adult to infant doses for liver and red bone marrow are 3.2 and 2.7, respectively. Lung doses to adults are about 1.3 times those to infants. The dose coefficients for 10-year-old children are less than 50% lower than the adult values for all tissues. Thus, most members of a population exposed to the same air concentration would receive roughly comparable doses.

**Table 3-12. Absorbed Dose Coefficients for Unit Exposure to Reference  $^{239}\text{PuO}_2$  Aerosols with AMAD =  $1 \mu\text{m}$ , GSD = 2.5<sup>a</sup>**

Organ or tissue	Absorbed dose coefficients for unit exposures to $^{239}\text{PuO}_2$ for persons of various ages ( $\mu\text{Gy} [\text{Bq h m}^{-3}]^{-1}$ ) <sup>b</sup>				
	1 year	5 years	10 years	15 years	Adult
Lung	3.0	3.1	3.5	3.5	3.8
Liver	0.53	0.80	1.1	1.3	1.7
Skeleton					
Bone surface	1.7	2.9	5.1	5.9	7.8
Red marrow	0.15	0.18	0.27	0.31	0.40

<sup>a</sup> Based upon [ICRP Publication 71 \(1995b\)](#)

<sup>b</sup> To convert values to ( $\text{mrad} [\text{nCi h m}^{-3}]^{-1}$ ), multiply by 3.7.

The values in [Table 3-12](#) are for normal breathing. As noted in [Chapter 2](#), inhalation rates for people performing heavy labor or exercising vigorously will be larger and will lead to higher intakes of plutonium. For those people, the dose coefficients per unit exposure will also be proportionally greater than the reference values shown in [Table 3-12](#).

The analysis of the critical group for exposures to plutonium released from Rocky Flats ([Chapter 2](#)) showed that there was little difference in risk for persons exposed as adults or while in their teens. A somewhat higher risk was identified for males than females because of higher risks of liver and bone cancer. Physical activity level and outdoor exposure at locations near

points of highest concentrations of airborne plutonium play a greater role in determining the overall risk. Age does play a role because older people were more likely to frequent locations of high air concentration because of suspension of plutonium from the 903 Area.

Realistic exposure scenarios are being developed for critical subgroups with hobbies or employment performed in the open air. Such behavior would enhance exposure to releases from the facility. Scenarios are also being developed for people with different lifestyles to show the range of doses and risks that could have occurred. Because the plutonium releases occurred at different times and had different characteristics (for example, particle size), the dose assessment effort will deal with exposure scenarios for the important releases. The scenarios will consider the appropriate characteristics of the plutonium aerosol and the activities (for example, breathing rate) of the representative member of the population to whom the scenarios apply.

### **3.6 Uncertainties in Plutonium Dose Estimates**

The dosimetry portion of the plutonium risk calculations will yield absorbed doses to organs and tissues of interest, normalized to a unit exposure as discussed above. These results will be linked with (a) estimates of risk per unit absorbed dose, the subject of much of this report, and (b) predictions of time-integrated air concentrations that are based upon source term and transport calculations. The first link will yield estimates of cancer risk per unit exposure and the corresponding uncertainties. The latter set of calculations, which will be performed for each of the most important releases from the RFP, are outside the scope of the present report.

There are several ways to examine the uncertainties associated with estimates of absorbed doses to the lung and other important body organs and tissues from inhalation of plutonium. One method involves considering the effect of choosing respiratory tract and biokinetic models for the behavior of plutonium in the body. We noted in [Section 3.2](#) that there have been some substantial changes in the models in recent years. A second method is to solicit the opinions of dosimetry experts regarding the reliability of the dose coefficients produced by the selected models. A third method is to perform a detailed parameter uncertainty analysis of the latest respiratory tract and biokinetic models used for state-of-the-art plutonium dose calculations. Each of these methods is considered below, beginning with the subjective evaluation of dose coefficients from the previous set of ICRP models.

#### **3.6.1 Subjective Uncertainty Analysis for Dose Estimates from ICRP Publication 30**

A measure of the uncertainties in the dose estimates provided by the previous set of ICRP models has been published. [Bouville et al.](#) (1994) obtained subjective uncertainty estimates for some of the dose coefficients, including those for  $^{239}\text{Pu}$ , in ICRP Publication 30 ([ICRP 1979](#)). They asked experts to quantify their views about the reliability of about two dozen important dose coefficients that were produced by the ICRP Publication 30 methodology.

The consensus of the experts was that the plutonium dose coefficients fell into a category that they termed “low reliability.” For doses to adult males, this level of reliability was characterized by a subjective 90% confidence interval that ranged from 10 times less than the central estimate to 10 times higher than that value. If the distribution of dose estimates were considered to be lognormal, the uncertainty for the subjective confidence interval would be consistent with a GSD for that distribution of about 3.3.

For special groups who might receive higher doses for one or more reasons, the experts estimated a subjective 90% confidence interval that covered a range defined by the central value multiplied or divided by a factor of 20. If we again consider the distribution of dose estimates to be lognormal, the GSD for the distribution would be about 4.5.

This subjective assessment of dosimetric uncertainties does not apply directly to the current ICRP models. However, it does provide an interesting perspective on the reliability of dose estimation procedures. A more complete report of the work of this committee has been published by the [NCRP](#) (1998).

### 3.6.2 Uncertainties Due to Model Selection

The models of ICRP Publication 30 ([ICRP](#) 1979) discussed above served as the standard method of dose estimation for more than 15 years. The respiratory tract model ([ICRP](#) 1966) was a very important component for evaluating inhalation exposures, and it provided the basis for dose estimation for nearly 30 years. Both the respiratory tract model and the biokinetic model for plutonium have been replaced by new, more complex models that are conceptually more realistic.

It is reasonable to ask about the effects of adopting the new models. Table 3-13 compares representative adult dose coefficients that were estimated using the old ([ICRP](#) 1979) and the new ([ICRP](#) 1994) models. Plutonium dioxide was listed as a Class Y aerosol in ICRP Publication 30; it is now treated as Type S under the newer modeling scheme. Table 3-13 compares dose coefficients for PuO<sub>2</sub> in columns 2 and 3. It can be seen that the lung doses from PuO<sub>2</sub> are estimated to be ~3.6 times lower using the new model and that the doses to liver and tissues in the skeleton are 5–8 times lower than those estimated previously. The final two columns compare results for the more soluble forms of plutonium, such as plutonium nitrate, considered to be in Class W in the old scheme and now treated as Type M. The differences are less striking. With the exception of the bone marrow, the new estimates are within a factor of 2 of previous values.

**Table 3-13. Comparison of Absorbed Dose Coefficients for Unit Intakes of Reference <sup>239</sup>Pu Aerosols**

Organ or tissue <sup>a</sup>	Absorbed dose coefficients (μGy Bq <sup>-1</sup> ) for unit intakes of <sup>239</sup> Pu in a reference aerosol with 1-μm median diameter			
	ICRP 30 Class Y	ICRP 71 Type S	ICRP 30 Class W	ICRP 71 Type M
Lung	16	4.4	0.84	1.6
Liver	10	2.0	26	16
Skeleton				
Bone surface	48	9.0	120	75
Red marrow	3.8	0.46	10	3.7

The range of values is the focus of our interest here, particularly for PuO<sub>2</sub>, the principal chemical form of plutonium in Rocky Flats releases. These comparisons do not provide any information about the accuracy of the estimates of doses to the tissues. It is natural to think that the newer models will produce better estimates of the doses. However, this expectation has not been tested.

A committee of the NCRP has also been developing a new detailed lung model for the respiratory tract ([Phalen et al. 1991](#); [Moss and Eckerman 1991](#); [Chang et al. 1991](#)) and a report has now been published ([NCRP 1997a](#)). The NCRP model is in some ways similar to and in other ways rather different from the ICRP model. The NCRP report includes only some example calculations of lung tissue doses following an accidental inhalation. Differences in model structure preclude definitive comparisons except for the deep lung (AI region of the ICRP model).

[Jarvis and Bailey \(1997\)](#) have compared the results for  $^{239}\text{Pu}$  given in the NCRP report with calculations made using the ICRP model. For a standard aerosol ( $d_{ae} = 1 \mu\text{m}$ ), they found that the deep lung doses predicted by the two models differ by less than a factor of 1.5. For the bronchial tree, they found that the ICRP model predicts distinctly higher doses (by more than a factor of 5), than those estimated by the NCRP model. This difference was due primarily to the inclusion of the slow clearance pathway in the ICRP model. The ICRP lung model was used in our analysis.

Overall, we have estimated that the ICRP model predicts a weighted lung dose that would be about 6 times higher than that obtained using the NCRP model and the assigned fractions in [Table 3-7](#). As noted, this is only an approximate comparison because of differences in model structure.

### 3.6.3 Parameter Uncertainties

The third method to uncertainty analysis cited above is to perform a parameter uncertainty analysis; that is, to assess the effects on the predicted dose coefficients that are due to uncertainties in the input parameters. This approach also includes identifying input parameters that are the most important contributors to the uncertainty in the computed dose coefficients.

Many parameters must be specified to calculate doses to the respiratory tract and to other organs and tissues that have been described above. These may be separated into categories in several ways. For example,

- Parameters used to characterize the plutonium aerosol
- Respiratory tract model and dosimetry parameters
- Parameters of the biokinetic model that govern distribution of plutonium to and its retention in other tissues
- Parameters that describe the radiosensitive cells in other body organs and tissues and their locations relative to plutonium deposits.

Many of the relevant parameters have been described above in the discussion of the respiratory tract model, the biokinetic model for plutonium, and the dosimetry models. A more detailed discussion of parameters in each of these categories follows.

Discussions of estimates of dose and uncertainty in this section refer implicitly to the context of the ICRP models. Model development by various ICRP working groups represents a substantial amount of effort and reflects a substantial body of expert opinion in a range of disciplines.

**3.6.3.1 Aerosol Characteristics.** To assess doses from exposure to a particular aerosol, the particle size distribution and the absorption type, which is related to chemical form, must be specified. Few aerosols consist of particles that are all the same size, density, and shape. Distributions of particle sizes are typically considered to be lognormal and are characterized by

their aerodynamic diameters and GSD. The limited information about particle size characteristics for the releases of interest at Rocky Flats is described in [Chapter 2](#).

The predominant chemical form of emissions from fires and from most routine operations was plutonium dioxide, which is represented by absorption type S. As noted in [Chapter 2](#), some of the plutonium released from the 903 Area may have been of absorption type M. This suspicion is not based upon measurements of solubility of particles in lung fluids or a sophisticated analysis. However, it is known that the barrels contained oil sludge and carbon tetrachloride and that there was opportunity for chemical changes to have occurred in the barrels. After leakage, there was additional time for changes in the environment before the plutonium was made airborne and carried to points of public exposure.

**3.6.3.2 Respiratory Tract Model and Dosimetry Parameters.** This large group of parameters, which encompasses those that affect estimates of particle deposition and clearance as well as lung morphology and physiology, is grouped together because [Huston](#) (1995) analyzed uncertainties in lung dosimetry using the new ICRP model of the respiratory tract ([ICRP](#) 1994). This section summarizes, in rather general terms, critical issues about the respiratory tract model parameters and those needed for lung dosimetry. A single issue may be affected by several parameters; discussions of individual parameters are provided in subsequent sections.

What follows is a brief summary of the findings most relevant to the dosimetry questions being addressed in this analysis. Following short-term exposures, the distributions of lung doses that resulted from including all the parameter uncertainties in the calculations of dose were approximately lognormal in shape. A 90% confidence interval for the dose distribution would range from the 5th to the 95th percentile value; 5% of the dose estimates would be below and 5% would be above the values. For polydisperse aerosols of  $^{239}\text{Pu}$  dioxide with median diameters up to 10  $\mu\text{m}$ , the ratio of the 95th to the 5th percentile value, both from the distribution of lung dose to adults, was found to lie between 5 and 10. The ratio was greater (closer to 10) for larger particle diameters (closer to 10  $\mu\text{m}$ ). Uncertainties were found to be greatest for exposure during light exercise, and the uncertainties associated with activity level were greater than those for variations in age and gender.

Breathing rate has an important affect on the magnitude of the dose received from a particular exposure. [Huston](#) (1995) found that for acute (short-term) exposures, dose was quite sensitive to ventilation rate. This finding would apply to doses from relatively short-term releases, possibly including the mechanical disturbance and high wind episodes that affected the 903 Area. It would not apply to longer term exposures (to routine releases, for example).

Particle deposition within the respiratory tract is clearly an important factor in lung dosimetry and this fact was confirmed by [Huston's](#) analysis. As indicated in the description of the deposition model ([ICRP](#) 1994), an uncertainty parameter has been included ( $c$  in the [Equation \[3-1\]](#)). For submicron particles, values of  $c$  are  $\sim 1.5$ ; for larger particles,  $c$  is generally on the order of 2–3.

The rates of clearance of material from the several respiratory tract compartments are important factors that affect the magnitudes of the doses to tissues in those compartments. For a particular compartment, the clearance rate depends upon the physical removal of particles and the removal by absorption into the blood. The sensitivity analysis performed in [Huston](#) (1995) found that both components of the clearance were important contributors to lung dose uncertainty.

Because the largest amounts of energy released when  $^{239}\text{Pu}$  decays are carried by alpha particles, the physical separation between the activity and the target cells is very important. The dimensions of the structural models of the type shown in [Figure 3-6](#) (presented earlier) are a very important part of the dosimetric analysis. In the extreme, target cells will not be irradiated if the thickness of tissue between the source particle and the cell layer exceeds the range of the alpha particle. [Huston](#) (1995) reviewed the reference values for the model and found a basis for a significantly thinner layer of bronchial epithelium than the ICRP default value. Including the lower estimates of tissue thickness leads to a larger fraction of alpha particle energy absorbed in the target cells.

**3.6.3.3 Parameters for the Biokinetic Model.** Tables [3-5](#) and [3-6](#) summarize the deposition fractions in various tissues for plutonium activity that reaches the bloodstream and the clearance rates for the current biokinetic model. While these values reflect the consensus expert opinions of a number of individuals, the variability of individual opinion is not included with the default values.

The values are not all independent and some relate to other parameters that are not prominent. The fraction of the material that goes to ST 1 is determined by difference, so its value could vary substantially depending upon the uncertainty distributions assigned to other parameters. The sum of all the tissue deposition fractions cannot exceed unity, which limits the possible range of individual components. In the current age-dependent model, the ICRP has consistently taken the sum of the liver and bone deposition fractions to be 80% of the activity reaching the blood and has varied the ratio with age depending upon the rate of bone formation. The confidence in the sum of the two fractions seems to exceed that in either one individually.

Estimates of the plutonium activity that reaches the blood are dependent on the parameters of the respiratory tract model. This is one area that [Huston](#) did not investigate, but the parameter distributions that he developed are used for that analysis. As noted in [Table 3-3](#), the fraction of the activity reaching the blood is more sensitive to absorption type than to particle size. [Table 3-14](#) contains the deposition fractions ( $f_d$ ) for the various respiratory tract clearance compartments (see [Figure 3-3](#)). [Table 3-14](#) shows both the ICRP reference values and the distribution or equation used in the Monte Carlo calculations. The parameters are generally taken to be lognormally distributed. An exception is the error term for the slow cleared fraction ( $f_s$ ), which is taken to be normally distributed. Because the three AI compartments are included in the clearance model only to reflect time dependence of the mechanical clearance from that region, it is not considered appropriate to vary all the parameters ([Bailey and Roy](#) 1994). Thus, no variation in  $f_d$  ( $\text{AI}_3$ ) is considered.

[Table 3-15](#) contains the parameter distributions assigned to the respiratory tract clearance rates that are shown in [Table 3-1](#) for the clearance pathways illustrated in [Figure 3-4](#). Consistent with [Bailey and Roy](#) (1994), the uncertainty in the clearance rate  $m_{1,4}$  is considered to be included in the uncertainty in the deposition fraction for that compartment [ $f_d$  ( $\text{AI}_1$ ) in [Table 3-14](#)].

**Table 3-14. Partition Fractions for Material Deposited in ICRP Lung Model Compartments**

Clearance compartment	Model parameter	Reference value	Equation used or characteristics of parameter distribution <sup>a,b</sup>
ET <sub>2</sub>	f <sub>d</sub> (ET <sub>2</sub> )	0.9995	f <sub>d</sub> (ET <sub>2</sub> ) = 1 - f <sub>d</sub> (ET <sub>seq</sub> )
ET <sub>seq</sub>	f <sub>d</sub> (ET <sub>seq</sub> )	0.0005	LN: GM = 0.0005, GSD = 1.73
BB <sub>1</sub>	f <sub>d</sub> (BB <sub>1</sub> )	0.993 - f <sub>s</sub>	f <sub>d</sub> (BB <sub>1</sub> ) = 1 - f <sub>s</sub> - f <sub>d</sub> (BB <sub>seq</sub> )
BB <sub>2</sub>	f <sub>d</sub> (BB <sub>2</sub> )	f <sub>s</sub>	f <sub>d</sub> (BB <sub>2</sub> ) = f <sub>s</sub> + E (f <sub>s</sub> ); N: m = 0, s = 0.1
BB <sub>seq</sub>	f <sub>d</sub> (BB <sub>seq</sub> )	0.007	LN: GM = 0.007, GSD = 1.73
bb <sub>1</sub>	f <sub>d</sub> (bb <sub>1</sub> )	0.993 - f <sub>s</sub>	f <sub>d</sub> (bb <sub>1</sub> ) = 1 - f <sub>s</sub> - f <sub>d</sub> (bb <sub>seq</sub> )
bb <sub>2</sub>	f <sub>d</sub> (bb <sub>2</sub> )	f <sub>s</sub>	f <sub>d</sub> (bb <sub>2</sub> ) = f <sub>s</sub> + E (f <sub>s</sub> ); N: m = 0, s = 0.1
bb <sub>seq</sub>	f <sub>d</sub> (bb <sub>seq</sub> )	0.007	LN: GM = 0.007, GSD = 1.73
AI <sub>1</sub>	f <sub>d</sub> (AI <sub>1</sub> )	0.3	LN: GM = 0.3, GSD = 1.41
AI <sub>1</sub>	f <sub>d</sub> (AI <sub>2</sub> )	0.6	f <sub>d</sub> (AI <sub>2</sub> ) = 1 - f <sub>d</sub> (AI <sub>1</sub> ) - f <sub>d</sub> (AI <sub>3</sub> )
AI <sub>1</sub>	f <sub>d</sub> (AI <sub>3</sub> )	0.1	0.1 (see text)
BB <sub>i</sub> and bb <sub>i</sub>	f <sub>s</sub>	Computed	d <sub>e</sub> ≤ 2.5 μm, f <sub>s</sub> = 0.5 d <sub>e</sub> > 2.5 μm, f <sub>s</sub> = 0.5 exp[-0.76(d <sub>e</sub> - 2.5)]

<sup>a</sup> LN = lognormal distribution; GM = geometric mean; GSD = geometric standard deviation; N = normal distribution; m = mean; s = standard deviation (based upon [Huston](#) 1995).

<sup>b</sup> The fraction (f<sub>s</sub>) that is cleared slowly from the various BB<sub>i</sub> and bb<sub>i</sub> compartments is considered to be dependent on particle size.

**Table 3-15. Uncertainty Distributions for Respiratory Tract Clearance Rates**

Clearance parameter <sup>a</sup>	Reference value	Characteristics of distribution <sup>b</sup>
m <sub>1,4</sub>	0.02	0.02 (see text)
m <sub>2,4</sub>	0.001	LN: GM = 0.001, GSD = 1.41
m <sub>3,4</sub>	0.0001	LN: GM = 0.0001, GSD = 1.73
m <sub>3,10</sub>	0.00002	LN: GM = 0.00002, GSD = 1.41
m <sub>4,7</sub>	2	LN: GM = 2, GSD = 1.41
m <sub>5,7</sub>	0.03	LN: GM = 0.03, GSD = 1.73
m <sub>6,10</sub>	0.01	LN: GM = 0.01, GSD = 1.73
m <sub>7,11</sub>	10	LN: GM = 10, GSD = 1.22
m <sub>8,11</sub>	0.03	LN: GM = 0.03, GSD = 1.73
m <sub>9,10</sub>	0.01	LN: GM = 0.01, GSD = 1.73
m <sub>11,15</sub>	100	LN: GM = 100, GSD = 1.73
m <sub>12,13</sub>	0.001	LN: GM = 0.001, GSD = 1.73
m <sub>14,16</sub>	1	LN: GM = 1, GSD = 1.73

<sup>a</sup> Subscripts refer to compartments in the model shown in [Figure 3-3](#).

<sup>b</sup> LN = lognormal distribution; GM = geometric mean; GSD = geometric standard deviation (based upon [Huston](#) 1995).

The upper portion of Table 3-16 contains the distributions of the parameters that are the basis for rate constants that describe the transport of material from the clearance compartments in [Figure 3-3](#) to the blood. The model for this process is shown in [Figure 3-4](#). The model applies to each of the compartments in the respiratory tract, and the process competes with mechanical clearance for removal of the deposited material. The lower part of the table shows the equations used to compute the rate constants for that model.

**Table 3-16. Parameters Describing Transport of Plutonium into Blood**

Symbol	Description	Reference value	Characteristics of distribution <sup>a</sup>
$f_r$	Fraction of material that is rapidly dissolved	0.001	LN: GM = 0.001, GSD = 3.2
$s_r$	Absorption/dissolution rate for fast phase	100 d <sup>-1</sup>	LN: GM = 100 d <sup>-1</sup> , GSD = 3.2
$s_s$	Absorption/dissolution rate for slow phase	0.0001 d <sup>-1</sup>	LN: GM = 0.0001 d <sup>-1</sup> , GSD = 3.2
$s_p$	Clearance rate from initial state to blood	0.01 d <sup>-1</sup>	Equation for calculation $s_p = s_s + f_r (s_r - s_s)$
$s_{pt}$	Clearance rate from initial state to transformed state	100 d <sup>-1</sup>	$s_{pt} = (1 - f_r) (s_r - s_s)$
$s_t$	Clearance rate from transformed state to blood	0.0001 d <sup>-1</sup>	$s_t = s_s$

<sup>a</sup> LN = lognormal distribution; GM = geometric mean; GSD = geometric standard deviation (based upon [Huston 1995](#)).

Table 3-17 contains the estimated uncertainty distributions for the fractions of plutonium deposited in the body tissue compartments. A rather broad range of values is considered, reflecting the wide range of values that have been used over the years for the fractions going to liver and bone.

**Table 3-17. Estimated Uncertainties in Tissue Deposition Fractions**

Tissue compartment (symbol)	Reference value	Distribution parameters or relationship for calculation
Cortical bone surface ( $f_{cb}$ )	0.3	$f_{cb} = 0.5 - f_{tb}$
Trabecular bone surface ( $f_{tb}$ )	0.2	$f_{tb} = k (0.8 - f_L)$ k: Uniform: 0.3–0.5
Liver 1 ( $f_L$ )	0.3	Uniform: 0.2–0.4
Gonads ( $f_g$ )	0.001% g <sup>-1</sup> of tissue	LN: GM = 0.001, GSD = 1.7
Kidney, urinary path ( $f_{ku}$ )	0.01	Uniform: 0.005–0.015
Kidney 2 ( $f_{k2}$ )	0.005	Uniform: 0.0025–0.075
Urinary bladder ( $f_b$ )	0.02	Uniform: 0.01–0.03
Soft tissue, slow turnover ( $f_{ST2}$ )	0.02	Uniform: 0.01–0.03
Soft tissue, intermediate ( $f_{ST1}$ )	0.12	<sup>a</sup>

<sup>a</sup> Computed by difference after considering all other compartments.

Table 3-18 contains our estimates of the uncertainties in compartmental clearance half-times for the various tissues. Uniform distributions were selected as being most appropriate for the clearance half-times although other forms, such as triangular, could also be considered.

**Table 3-18. Uncertainty Distributions for Clearance Half-times for Plutonium**

Plutonium clearance route		Reference	Uniform distribution
From	To	half-time ( $\tau$ , d)	range (d)
Cortical bone surface	Cortical bone volume	16,900	15,000–19,000
Cortical bone surface	Cortical bone marrow	8,440	7,000–10,000
Cortical bone volume	Cortical bone marrow	8,440	7,000–10,000
Trabec. bone surface	Trabec. bone volume	2,810	2,100–3,500
Trabec. bone surface	Trabec. bone marrow	1,410	1,000–1,800
Trabec. bone volume	Trabec. bone marrow	1,410	1,000–1,800
Either bone marrow	Blood	91	70–110
Liver 1	Liver 2	390	300–500
Liver 1	Small intestine	5,200	3,900–6,500
Liver 2	Blood	3,300	2,500–4,100
Soft tissue 0	Blood	1	0.75–1.25
Soft tissue 1	Blood	1,460	1,000–1,900
Soft tissue 1	Urinary bladder	1,460	1,000–1,900
Soft tissue 2	Blood	36,000	30,000–42,000
Ovaries or testes	Blood	3,600	2,400–4,800
Kidney, urinary path	Urinary bladder	50	25–75
Kidney 2	Blood	500	400–600

**3.6.3.4 Dosimetric Parameters for Body Tissues.** For many tissues the plutonium is assumed to be fully intermingled with the sensitive tissues, which may not be well defined. This leads to an assumed maximum absorbed fraction of unity, as is the practice for the liver. The mass of the sensitive tissue is then the mass of the entire organ. Uniform distributions are used to estimate the absorbed fractions for endosteal cells in bone. Values ranging from 70 to 130% of the reference values in [Table 3-10](#) are used in the calculations. Central estimates of tissue masses for the liver and tissues in the skeleton ([Table 3-8](#)) are assumed to be medians of lognormal distributions with GSDs of 1.3.

**3.6.3.5 Estimates of Uncertainty in Dose Coefficients.** The parameter distributions presented above have been used in Monte Carlo calculations of uncertainty in the dose coefficients for the liver and for tissues in the skeleton. Estimated dose coefficients and their uncertainties are presented in [Tables 3-19](#), [3-20](#), and [3-21](#) for aerosols with AMADs of 1 $\mu$ m, 5 $\mu$ m, and 10  $\mu$ m, respectively. The distributions of dose coefficients are approximately lognormal and each is characterized by a median value and the associated GSD. Uncertainties in dose coefficients for tissues other than lung have been increased to account for modeling uncertainties that may not be adequately reflected in the parameter uncertainties discussed above. As noted previously, uncertainties in lung dose coefficients are taken from [Huston](#) (1995). These results are used together with predicted environmental concentrations, behavior scenarios, and risk coefficients to estimate distributions of risks associated with plutonium exposures for particular Rocky Flats release events.

### 3.7 Summary

This chapter describes the most recent ICRP models of deposition of plutonium in the respiratory tract, its removal from deposition sites, and its transport to other body tissues. These models are combined with models of alpha particle dosimetry to provide estimates of dose coefficients ( $\mu\text{Gy Bq}^{-1}$ ) and the uncertainties associated with these estimates. The calculations depend upon the particle size that characterizes the aerosol to which a person was exposed. Dose coefficients and uncertainties have been estimated for adults exposed to aerosols with AMADs of 1, 5, and 10  $\mu\text{m}$ . These are presented in Tables 3-19, 3-20, and 3-21. This range of particle sizes addresses exposures to a variety of releases from Rocky Flats. In general, the cells lining bone surfaces receive the highest doses following plutonium inhalation. Doses to the lung and to the liver are lower by factors of 2–5. Doses to bone marrow are substantially smaller.

**Table 3-19. Estimated Dose Coefficients per Unit Intake of  $^{239}\text{PuO}_2$  Aerosol with AMAD = 1  $\mu\text{m}$  and GSD = 2.5**

Target tissue	Median dose coefficient <sup>a</sup> ( $\mu\text{Gy per Bq inhaled}$ )	Geometric standard deviation
Lung	4.4	1.9
Liver	2.0	3
Bone surfaces	9.0	3
Bone marrow	0.46	3

<sup>a</sup> The median dose coefficients of the uncertainty distributions for each tissue agree well with the point estimates given by ICRP 1995b, Table 5.29.3c that are based on the same models. ICRP 1995b provides equivalent dose coefficients that assume an RBE of 20.

**Table 3-20. Estimated Dose Coefficients per Unit Intake of  $^{239}\text{PuO}_2$  Aerosol with AMAD = 5  $\mu\text{m}$  and GSD = 2.5**

Target tissue	Median dose coefficient ( $\mu\text{Gy per Bq inhaled}$ )	Geometric standard deviation
Lung	2.6	2.7
Liver	0.95	3.5
Bone surfaces	4.6	3.5
Bone marrow	0.22	3.5

**Table 3-21. Estimated Dose Coefficients per Unit Intake of  $^{239}\text{PuO}_2$  Aerosol with AMAD = 10  $\mu\text{m}$  and GSD = 2.5**

Target tissue	Median dose coefficient ( $\mu\text{Gy per Bq inhaled}$ )	Geometric standard deviation
Lung	1.2	4.3
Liver	0.42	4.5
Bone surfaces	2.1	4.5
Bone marrow	0.11	4.5

## 4. EPIDEMIOLOGY AND THE BASIS FOR RISK ESTIMATION

Epidemiological investigations provide the basis for estimating the risks of cancer induced by radiation in man. A vast literature on the effects of radiation has developed as a result of exposures at work, in the home or in the environment, as well as in medical procedures and atomic explosions. This literature continues to grow and is assessed at intervals by committees such as UNSCEAR and the U.S. BEIR committees of the National Academy of Sciences. Additionally, the ICRP and the NCRP in the U.S. evaluate UNSCEAR and BEIR reports and often further assess the literature to formulate risk estimates as the basis for recommendations on limiting exposure for radiation protection. National regulatory agencies such as the EPA have used the work of the BEIR committees and advisory bodies such as ICRP and NCRP to develop their own risk factors ([Puskin and Nelson](#) 1995) and for risk based standards.

All of these bodies have relied primarily on the LSS of the survivors of the atomic bombs dropped at Hiroshima and Nagasaki in 1945 for their estimates of the risk of induced cancer to the whole body or to individual organs from low-LET gamma radiation. Studies of medical and occupational exposure to radiation have supplemented the LSS and for some organs and tissues have provided unique information. Studies of radon exposure and of radium and thorium isotopes in humans have yielded information on alpha-emitter exposures in selected organs.

Laboratory studies in radiation biology of cellular and animal systems have also provided important information relating to risk estimation, especially on ratios between the effectiveness of different radiations (the RBE) and on the effects of dose and dose rate on the response. Genetic effects have also been studied primarily in the laboratory especially in the fruit-fly (*drosophila*) and the mouse.

This chapter provides some important considerations relating to epidemiology and some features of risk estimation especially at low doses as background to the four approaches to plutonium risk estimation. The approaches are illustrated in [Figure 1-2](#) and discussed in detail in Chapters [5](#) through [8](#).

### 4.1 Measures of Risk

The discussion in this section is based on, but adapted and modified from [UNSCEAR](#) (1994), Annex A. It is included here to explain the more common methods used to describe risks of radiation effects. As used here, risk is the probability of a harmful event, specifically cancer induction.

In epidemiology, late radiation effects are described in terms of simple measures of the excess risk. The most commonly used are relative and absolute risk estimates. If  $O$  is the number of cancers observed in a population and  $E$  is the number of cancers expected in the population in the absence of exposure, the relative risk ( $RR$ ) is defined as

$$RR = \frac{O}{E} \quad (4-1)$$

and the excess risk ( $ER$ ) is defined as

$$ER = O - E. \quad (4-2)$$

A most useful quantity for comparison is the excess relative risk (*ERR*), defined as

$$ERR = \frac{O}{E} - 1 = \frac{O - E}{E} . \quad (4-3)$$

To compare estimates derived from different exposed populations, it is useful to define risks per unit dose, or risk coefficients. Thus, if *D* is the average dose received by an exposed population, the linear excess relative risk coefficient is defined as

$$ERR_D = \frac{O - E}{ED} . \quad (4-4)$$

The symbol *D* is most often used to represent absorbed dose to an organ or tissue (in grays). A weighted dose (in sieverts), with neutron RBE = 10, is frequently used for the atomic bomb survivors. Note that ICRP recommends an RBE of 20 for neutrons at very low doses ([ICRP 1991](#)) but the atomic bomb survivors cover a broad range of doses for which an RBE of 10 is more appropriate. As noted in RERF reports (e.g. [Pierce et al. 1996a](#)) the value of neutron RBE is not important in risk estimation as long as the neutron component is a small fraction of the total dose.

To compare values for the excess absolute risk in different studies, it is necessary to consider the dose, the size of the exposed group, and the length of time that the group has been studied. This may be done through the use of the excess absolute risk coefficient (*EAR*) per unit dose and per unit time at risk, i.e., the *EAR<sub>D</sub>* is given by

$$EAR_D = \frac{O - E}{PYD} \quad (4-5)$$

where *P* is the number of persons involved and *Y* is the number of years of follow-up.

The symbols *ERR<sub>1Gy</sub>* or *EAR<sub>1Gy</sub>* and *ERR<sub>1Sv</sub>* or *EAR<sub>1Sv</sub>* are also used to represent the excess relative or excess absolute risk coefficients per unit dose at 1 Gy or 1 Sv, respectively. The *EAR* per 10,000 PYGy or per 10,000 PYSv is a term often used to describe the absolute risk (per year and per gray or sievert) over the period of observation.

Often a more useful quantity than the excess absolute risk over the period of observation is the (absolute) lifetime risk due to the exposure. This is a measure of the total induced cancer risk over the lifetime of the population because of the exposure. It requires either follow-up of the population through an entire lifetime or projection of the risk for the period of observation to the lifetime risk. Lifetime follow-up is in progress with the LSS of the atomic-bomb survivors, but it is still incomplete; 61% of the survivors were still alive in the 1985 evaluation and 56% were alive at the time of the 1990 evaluation ([Pierce et al. 1996a](#)).

Methods for projecting the risk from the period of observation to the lifetime risk are discussed in UNSCEAR and some alternatives to projecting via constant relative risk with time in order to allow for possible declining risk with time were considered. The method preferred at that time (1994) was still to use the constant relative risk projection.

In recent years there have been numerous papers suggesting that cancer risks decline with time after exposure. This decline seems to be definite for those exposed in childhood both in the

LSS ([Pierce et al. 1996a](#)) and in other studies ([Little et al. 1991](#)) but less certain for cancer induction after adult exposures. For adults there is a relatively dramatic loss of solid tumor risk with time in the ankylosing spondylitis patients ([Darby et al. 1987](#)) whereas in the LSS, declines with time are more debatable. For some individual tumors such as breast and lung the BEIR V committee ([NAS/NRC 1990](#)) used models in which the risk declined with time.

However, a recent paper by [Preston et al. \(1997\)](#) emphasizes that for all solid tumors the percentage of attributable cancer deaths has not declined sensibly between the 1985 and 1990 evaluations of the LSS (4.5% versus 4.4%). It would seem that this point will eventually clarify itself but in the meantime considerable uncertainty must be associated with the projection of the observed risk to lifetime risk and must be accounted for in the overall uncertainties of a given lifetime risk estimate ([NCRP 1997b](#)).

More than one kind of lifetime risk estimate can be defined. For example, one measure of lifetime risk is the risk that an individual would die of a cancer that arose because of the exposure in question, known as the risk of exposure induced death (REID). This definition is most often used in UNSCEAR reports. Another quantity, however, is the excess lifetime risk (ELR) defined as the increase in lifetime risk of the cancer in question experienced by an individual as a result of the exposure. These quantities are not quite the same. The REID includes cases that would have died of cancer anyway but die earlier as a result of the exposure; the ELR does not. Thus, the ELR will generally be 15–20% less than the REID for all cancers combined but less different for individual cancers. BEIR committees have generally used the ELR. The REID and ELR are both measures of the lifetime detriment from radiation. Further discussion of the subject is given in [UNSCEAR \(1994\)](#).

**Table 4-1. Expected Life Lost per Fatal Cancer in Different Organs and Tissues or per Serious Genetic Effect**

Organs and tissues	Life lost (years) <sup>a,b</sup>
Bladder	9.8
Bone marrow	30.9
Bone surface	15.0
Breast	18.2
Colon	12.5
Liver	15.0
Lung	13.5
Esophagus	11.5
Ovary	16.8
Skin	15.0
Stomach	12.4
Thyroid	15.0
Remainder	13.7
Gonads	20.0

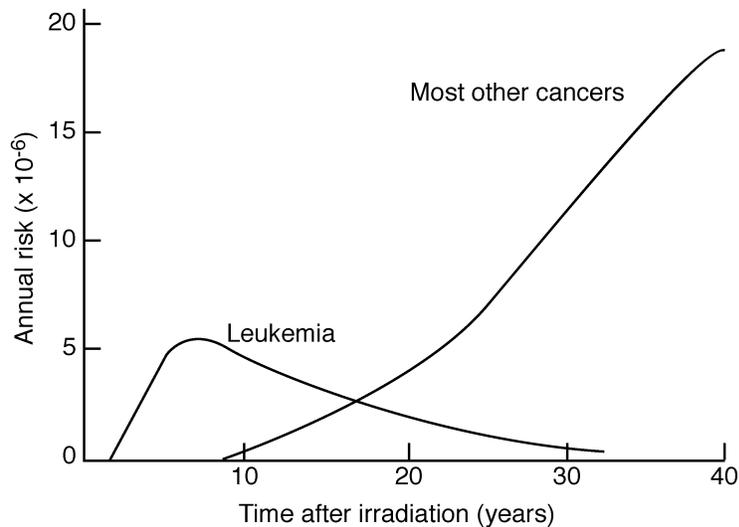
<sup>a</sup> Averaged for two models, gender and five national populations, age 0–90 years.

<sup>b</sup> From ICRP Publication 60, Table B-18 ([ICRP 1991](#)).

Neither the REID nor the ELR provide any information on the times at which exposure-induced events occur. This can be provided by an additional quantity known as the loss of life expectancy (LLE) due to the exposure. (This measure was used in the [UNSCEAR \[1988\]](#) report.) A more useful quantity still is *the years of life lost per radiation induced case (YLC)* obtained by dividing the LLE by the REID. Tables of the years of life lost for cancers in individual organs and tissues are given in ICRP 60, Table B-18 ([ICRP 1991](#)). The table is reproduced here as [Table 4-1](#). The average number of years of life lost per cancer induced ranges from about 10 (bladder cancer) to about 30 (leukemia). The average length of life lost is derived from the expected years of life lost for all cancers divided by the total number of fatal cancers, and equals 15 years. ICRP considered these differences in loss of life per individual cancer sufficiently important that they included an adjustment for the relative loss of life per cancer in the overall radiation health detriment ([ICRP 1991](#)).

## 4.2 Latency

It is commonly assumed that cancer arises initially from a change in a single cell. The altered cell then proliferates, and after many other alterations the cells become an overt cancer. This process takes time; consequently, there is always a latent period between the initiating event and the clinical detection of a cancer. This latent period or latency varies to a degree with the type of cancer. The radiation-induced cancer with the shortest latency is leukemia. The risk of fatality from leukemia in an irradiated population with the time after exposure is shown in Figure 4-1.



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**Figure 4-1.** Nominal risk of fatal cancer from a single dose of 10 mSv, uniform whole-body gamma irradiation versus time after acute exposure ([Sinclair 1993a](#)).

After 2 years, leukemia begins to rise and reaches a peak at 7–8 years and then declines to close to zero in 25–30 years. The average latency is about 10 years. Radiation-induced solid

tumors on the other hand have a minimum latency of about 10 years (more or less, depending on the type of tumor and the age, younger ages having shorter latency). The risk of a fatal tumor rises thereafter, roughly proportional to the natural rate of fatal cancer in an aging but unexposed population, also shown in Figure 4-1. It is not known yet whether the incidence of solid tumors subsequently declines after 45 years since the Japanese survivors of the atomic bombs, our main source for this information, have not yet been followed for long enough. Some solid tumors, such

**The time between exposure to radiation and clinical detection of a cancer is referred to as latency and varies with the type of cancer. Leukemias have the shortest latency.**

as thyroid tumors, have shorter minimum latency, about 5 years ([NIH](#) 1985) instead of 10 years and perhaps even shorter for young children (e.g. [NEA](#) 1995). Another solid tumor, osteo-sarcoma (bone tumors) follows more closely the time relationship for expression given by leukemia in [Figure 4-1](#), declining earlier than for other solid tumors. Thus, bone tumors would be expected to appear earlier than, for example, lung tumors in humans. However, it should be noted that in dogs the temporal patterns of tumor occurrence are

remarkably similar for lung and bone tumors and both precede liver tumors ([Muggenburg et al.](#) 1996).

Latency is sometimes related to dose, i.e. the higher the dose the shorter the latency. This may, however, be the result of the fact that more tumors occur at high dose and some of them are early giving an apparent shortening of the latent period compared with low doses. Latency may be more difficult to assess in exposure circumstances different from that given in [Figure 4-1](#) (i.e., acute exposure), for example, in protracted exposure with alpha emitters. Nonetheless latency between exposure and tumor occurrence is present in these circumstances also. In the evaluation of risk estimates, it is common practice to allow for latency by including an initial lag period in the analysis.

### 4.3 Incidence Versus Mortality

Many epidemiological studies rely on death certificate information and, thus, are based on mortality. Many others, however, derive from studies of cancer incidence usually based on direct contact with the affected individual through sources such as tumor registries. The numerical difference between incidence and mortality is small for some cancers for which survival is low (such as lung, liver, stomach, pancreas and leukemia). In others, for which survival is higher, the difference between incidence and mortality is large (such as female breast, uterus, thyroid, and skin) see [Table 4-2](#) for U.S. data (Table B-19 from [ICRP](#) 1991). Bone cancer survival rates are intermediate.

Studies of incidence that have been common in medical exposures (e.g., breast) ([UNSCEAR](#) 1994) have only recently become available in the LSS. These studies provide new and important information. Mortality studies rely on death certificates in which there are inherent biases (see [Section 6.3.1.2](#) on statistical biases including misclassification in the LSS). In incidence studies the diagnosis is much more certain and can be verified histologically, i.e., by microscopic examination of tumor tissue, but there is a problem of emigration of individuals from the study location. The number of

**The survival rate for lung and liver cancer is low therefore their mortality and incidence rates are very similar. For bone cancer the survival rate is higher and the incidence rate is about double the mortality rate.**

incident cases available will always be greater than the number of fatalities, perhaps many times more. In the LSS, the data on thyroid cancer incidence indicate a significant risk, whereas the mortality data have always failed to do so. In addition, incidence data provide earlier information, so it can be expected to be especially useful in evaluating the younger cohorts at Hiroshima and Nagasaki, for whom the risks are still quite uncertain.

**Table 4-2. Lethality Data for Cancers in Adults by Organ or Tissue**

Organ or tissue	Estimated lethality fraction $k$	
	U.S. data <sup>a</sup>	Colorado data <sup>b</sup>
Bladder	0.50	–
Bone	0.70	0.50
Brain	0.80	–
Breast	0.50	–
Cervix	0.45	–
Colon	0.55	–
Kidney	0.65	–
Leukemia (acute) <sup>c</sup>	0.99	0.75 <sup>d</sup>
All leukemia	–	0.81 <sup>d</sup>
All leukemia (without CLL)	–	0.76 <sup>d</sup>
Liver	0.95	0.98
Lung and Bronchus	0.95	0.96
Esophagus	0.95	–
Ovary	0.70	–
Pancreas	0.99	–
Prostate	0.55	–
Skin	0.002	–
Stomach	0.90	–
Thyroid	0.10	–
Uterus	0.30	–

<sup>a</sup> Numbers were derived from tables and graphical data for the U.S. by F.A. Mettler and W.K. Sinclair ([ICRP](#) 1991) based on 5-year (1980–1985) and 20-year (1950–1970) lethality data.

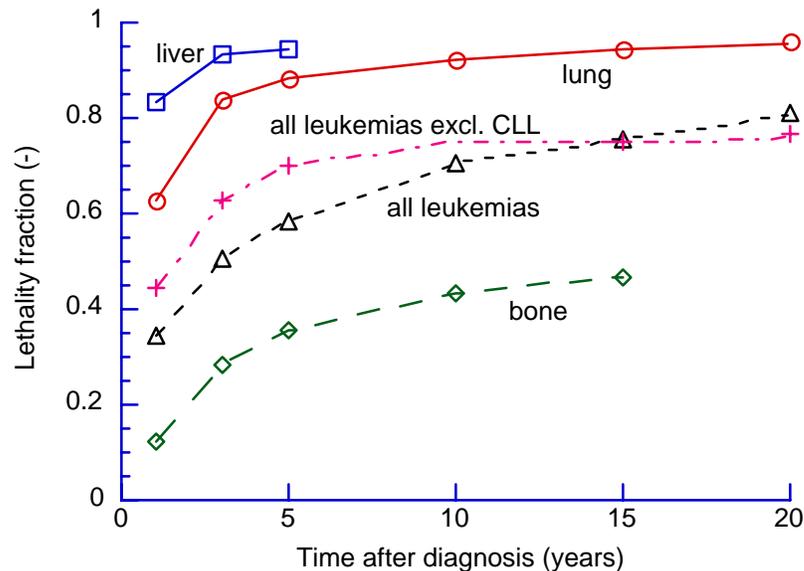
<sup>b</sup> Data for the State of Colorado (1974–1991); [Finch](#) (1996). See [Figure 4-2](#). (20-year values)

<sup>c</sup> U.S. data for adults; Colorado data for adults and children.

<sup>d</sup> Colorado data for adults and children.

If mortality data for cancer are available for a given organ or tissue, the incidence risks can be estimated by dividing the mortality rate by the *lethality fraction* given in [Table 4-2](#). This method is recognized as comparatively crude because lethality fractions are often based on data obtained much earlier which may already have altered. This limitation is especially true of organs with low lethality fractions such as skin and thyroid. In these cases, and perhaps generally, it is better, where good incidence data are available to use these data directly using life-table methods but this has rarely been done. An exception is the work of [Little et al.](#) (1997). For cancer in organs such as liver or lung with lethality fractions close to 1.00 this objection is less valid and this is the case with plutonium exposures considered in this report.

In environmental circumstances, as for plutonium in the form of oxide ( $\text{PuO}_2$ ) at Rocky Flats, cancer incidence rather than fatality is of primary concern to the public. Since plutonium in this chemical form causes mainly lung tumors, for which the lethality is high, incidence is only a little greater than mortality ([Table 4-2](#)). The lethality data for Colorado are determined from the survival data provided by the Colorado Department of Public Health and Environment ([Finch 1996](#)). These data, which are listed in [Table 4-2](#) and plotted in [Figure 4-2](#), are used in this report to convert risk of death to risk of incidence ([Section 9.4](#)). The most appropriate entry for leukemia is that for all leukemias excluding chronic lymphatic leukemia (CLL) because CLL is not believed to be induced by radiation ([Tomonaga et al. 1991](#); [Pierce et al. 1996a](#)). The entry for Colorado includes a population of all ages.



**Figure 4-2.** Lethality fraction versus time after diagnosis (State of Colorado data 1974–1994; [Finch 1996](#)). (For liver and bone the values at 20 years are obtained by extrapolation.)

#### 4.4 Limitations of Epidemiology

Epidemiological studies are essentially observational, i.e., they are guided by circumstances rather than experimental design. Thus, conditions of exposure, study population, existence of confounding factors, and many other features are beyond the control of the investigator. Some of these features must be accounted for by identifying and where possible eliminating or correcting for distortions because of extraneous factors. Wherever possible, control populations should meet conditions identical to those of the exposed population and share characteristics such as age, gender and ethnicity.

Cohort studies involve the follow-up of an exposed versus a control cohort for the incidence of diseases such as cancer or mortality from such diseases. They require many thousands of individuals in the study in order to detect the often small effects of exposure in increasing the natural rate of the disease and to assess the dependence of induced effects on age, gender, time

after exposure, etc. Cohort studies may have to continue over many years or decades for a full evaluation.

Although follow-up is often prospective many cohort studies begin with historical data that may not be complete especially in the early stages after exposure. It is also important to ensure that the relationship between disease rates and exposure (i.e., organ dose) is not distorted by unmeasured factors. The controls are always important and should be drawn from a group either the same or very similar to the exposed groups. For workers, for example, the controls must be other similar but unexposed working groups in order to account for the “healthy worker” effect. Comparisons with “national statistics”, for example, are rarely adequate.

Case control studies use individual controls matched as closely as possible in all respects to the exposed individuals in the study. A great advantage is that these studies require fewer cases but they also require even greater care in the selection of controls and whether or not these are truly representative of the population from which the cases themselves were selected. They are often useful as a subset of a cohort study to bring out a selected feature difficult to establish in the cohort study itself. They have been used in a variety of ways, for example, to assess the effect of radon exposure in homes on the lung cancer risk among persons of different smoking habits or the risk of radiation exposure and other risk factors in breast cancer induction in atomic bomb survivors or cervical cancer patients.

The existence of a causal relationship between exposure and effect is frequently difficult to demonstrate. The strength of the association between exposure and disease, the existence of a dose response relationship, and experimental evidence of similar effects in the laboratory are important factors in establishing a causal relationship. A list of factors important in demonstrating causal relationships includes strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy ([Hill](#) 1965).

All of the limitations of epidemiology are especially manifest in studies involving small exposures (low doses) to the general population from some environmental source. The general population is already exposed to natural sources of radiation from which the effective dose rate is 2–3 mSv  $y^{-1}$ . This is a small dose rate. Even environmental exposures giving rise to doses or dose rates several times this natural background may be very difficult to evaluate. Strict controls and evaluation of confounding factors become exceedingly important. There are inherent statistical limitations in quantitative effects after small doses. If a large number of significance tests are carried out, some findings will reach nominal significance (lower or higher) from chance alone ([UNSCEAR](#) 1994). If repeated observations are possible, they may demonstrate that chance was responsible but this may be difficult to prove. Finally, in the low dose region, when it becomes impossible to demonstrate clear evidence of an effect because of statistical limitations, this is not necessarily an indication that effects do not exist. Furthermore, even in the low dose region where effects are difficult to quantify, epidemiological studies can often provide upper limits to the magnitude of the risk.

#### **4.5 Transfer of Risk Estimates between Populations**

Another source of potential error and uncertainty arises in applying or transferring risk coefficients derived from the atomic bomb survivors to selected U.S. populations. The U.S. population has different cancer characteristics from those of the Japanese population. For example, the incidence of stomach cancer is low in the U.S. and high in Japan while for colon cancer the situation is reversed. One way to transfer a risk estimate is to transfer the same *ERR*

from one population to the other; this method makes use of the spontaneous rate for that cancer in the new population. Another is to transfer the *EAR* from one population to the other; this method does not use the spontaneous rate in the population. There is conflicting evidence about which transfer to use especially in the case of individual organs. In some organs it makes little difference which method is used; in other organs (those with very different spontaneous rates) it makes a large difference as shown by [Land and Sinclair](#) (1991). [Land and Sinclair](#) (1991) and subsequently [ICRP](#) (1991), averaged the results of the two methods to perhaps reduce possible errors in those organs where the differences were large. The result is that risks in individual organs for members of the U.S. population do not differ significantly from those risks derived by [ICRP](#), which were based on an analysis averaged over five populations ([NCRP](#) 1993b). EPA ([Puskin and Nelson](#) 1995) in re-examining these procedures also averaged the two methods but geometrically rather than arithmetically and obtained somewhat different results for some organs, such as the colon and stomach. While the evidence is not strong, some tumors seem to fit better a relative risk transfer (stomach) and others an absolute risk transfer (breast) (see [NCRP](#) 1997b). These differences at first seem strange but they may be accounted for by choosing appropriate models, as [Leenhouts and Chadwick](#) (1994) point out, in their application of a two mutation model to various aspects of carcinogenesis.

Transfer between populations is an important source of uncertainty in the final risk estimate, more for some organs than for others. For total cancer risk the uncertainty is somewhat less than for most organs ([Land and Sinclair](#) 1991). This subject is addressed further for the LSS in [Section 6.3.4](#) and in some detail in [NCRP](#) (1997b).

#### 4.6 Uncertainty in Risk Estimates

Risk estimates (more precisely, risk coefficients) are the ratio of an excess number of cancers per unit population to the dose causing them. In any assessment of a risk coefficient there will be uncertainty in determining the excess number of cancers against the fluctuating background of spontaneous cancers in all epidemiological circumstances. There may also be biases such as those resulting from misclassification of diseases other than cancer as cancer and vice versa. There will also be uncertainties in the dosimetry, especially since most often doses have to be reconstructed long after the event (as in the case of the survivors of the atomic bombs and in many environmental exposure circumstances). If the lifetime risk coefficient is the quantity sought, there will be further uncertainty in the projection of the risk observed over a period of years to the lifetime of the exposed population. If the risk coefficient was derived in a population other than that in which the exposures occurred, it will be necessary to transfer the risk from the exposed population to the new population. Uncertainty arises in the method of transfer because there is no assured method of making such a transfer. Further, uncertainty may arise if the physical circumstances of the exposure (e.g., the dose rate) are very different from the circumstances to which the risk coefficients are applied. Likewise, further uncertainty arises if the type of radiation being considered (e.g., alpha particle radiation) is different from the radiation (say gamma radiation) for which the risk estimates were obtained. All of these factors and some additional factors must be taken into account in a full assessment of the uncertainty relating to the use of risk coefficients in a given circumstance.

Some groups have made quantitative estimates of uncertainty in particular circumstances. For example the NIH working group that produced the radioepidemiological tables provided estimates of uncertainty for their estimates of probability of causation in a wide variety of

exposure circumstances ([NIH](#) 1985). Both UNSCEAR ([UNSCEAR](#) 1988) and BEIR V ([NAS/NRC](#) 1990) provided brief estimates of uncertainty in their evaluations of cancer risk. [Sinclair](#) (1993b) pointed out that because the derivation of lifetime risk estimates in the LSS of the atomic bomb survivors provided a clear dependence on five major factors, that evaluating uncertainty in each factor could lead to an estimation of the combined uncertainty in the overall lifetime risk. A preliminary estimate was made. The subsequent evaluation by NCRP of the uncertainties in fatal cancer risk estimates based on the LSS of the atomic bomb survivors and used for radiation protection ([NCRP](#) 1997b) is much more comprehensive. It gave a median lifetime risk coefficient for the U.S. population of  $3.38 \times 10^{-2} \text{ Sv}^{-1}$  where the 5th and 95th percentiles of the distribution ranged from  $1.2 \times 10^{-2} \text{ Sv}^{-1}$  to  $8.84 \times 10^{-2} \text{ Sv}^{-1}$ . The probability distribution was approximately lognormal. This latter report set the stage for evaluations of uncertainty in cancer risk for individual organs that are developed in this report in [Chapter 6](#).

#### 4.7 Age Dependence of Risk

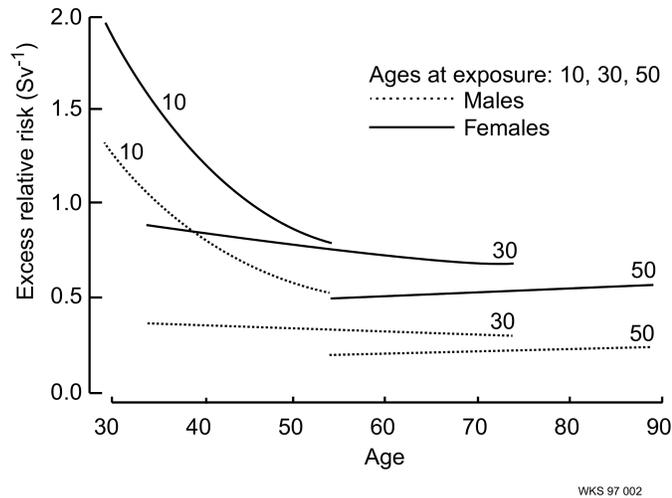
Some radioepidemiological studies are sufficiently large and comprehensive that subgroup analysis by age and gender is possible. This is the case for the LSS and for some studies of specific cancers induced by medical irradiation.

[Figure 4-3](#) shows the influence of age and gender on the risk of all solid cancers as determined by the 1950–1990 evaluation of the LSS ([Pierce et al.](#) 1996a). The figure shows both the *ERR* ([Figure 4-3a](#)) and the *EAR* ([Figure 4-3b](#)) for mortality from solid tumors as a function of attained age. The curves for *ERR* versus attained age indicate a decline in the risk of death for those exposed at age 10, which may eventually level out to constant *ERR*. This remains to be seen. The difference in gender is of the order of a factor of 2 in *ERR*, the risk for females being greater than that for males. The curves for *EAR* versus attained age ([Figure 4-3b](#)) show smaller age and gender differences. According to [Pierce et al.](#) (1996a), a single curve could be drawn through all ages and both genders with no statistically significant deviations. The gender difference is of the order of only 25–30%—mainly because of the differences in the background rates. These curves suggest that expressing risks in *EAR* rather than *ERR* could have significant advantages and would avoid overemphasizing differences in gender as the *ERR* tends to do. The situation is less clear for leukemia ([Figure 4-4](#)) where there are significant differences in risk depending on age at exposure and gender for both *ERR* and *EAR*.

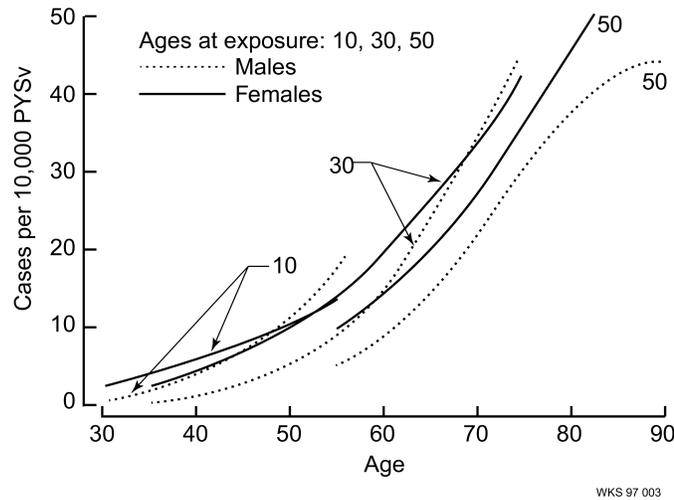
Age at exposure differences are also evident in a number of studies of the female breast in addition to the LSS. Most studies show a decline of *ERR* with age and the *ERR* at greater ages (above 40) tends to zero ([Figure 4-5](#)).

Lifetime risk involves accumulating the absolute risk over the remaining lifetime of the individual. Therefore if the risk continues throughout life persons exposed at younger ages have a longer period for expression and a declining lifetime risk versus age at exposure results. The form of this lifetime risk versus age response for solid tumors depends on the method that is employed for the projection to lifetime (see [Section 6.3.3](#)). In its 1994 report, UNSCEAR calculated lifetime risks of death for the population of Japan in 1985 based on the period of observation from 1950 to 1987. They used three slightly different methods for projection to lifetime: constant relative risk and two others with different declining risks. Lifetime risks are most often calculated assuming constant relative risk since this form of time response is still being closely followed in the LSS. Consequently, this projection is favored and will be used here (see [Chapter 6](#)). [Table 4-3](#) shows the UNSCEAR calculations of lifetime risk versus age at

exposure for constant relative risk after an exposure of 1 Sv. Although the numbers in [Table 4-3](#) could be used to adjust risk estimates as a function of age, they tend to exaggerate the precision with which age response information is known. Age response information is based on relatively few age groups. A simpler procedure may be more justified, for example, comparing the risk for those under 20 years of age with the risk of those over 20 years of age, as was done in [UNSCEAR](#) (1994) for tumors of specific organ and tissue sites ([UNSCEAR](#) 1994, Annex A, Table 8).

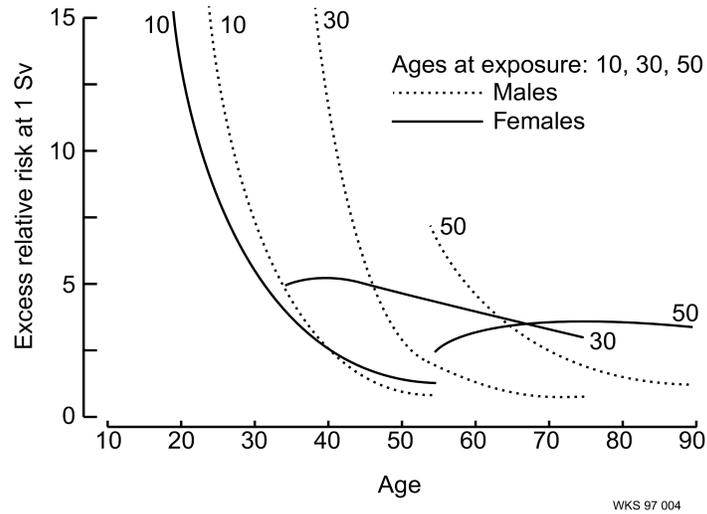


(a) Solid cancers: excess relative risk per sievert

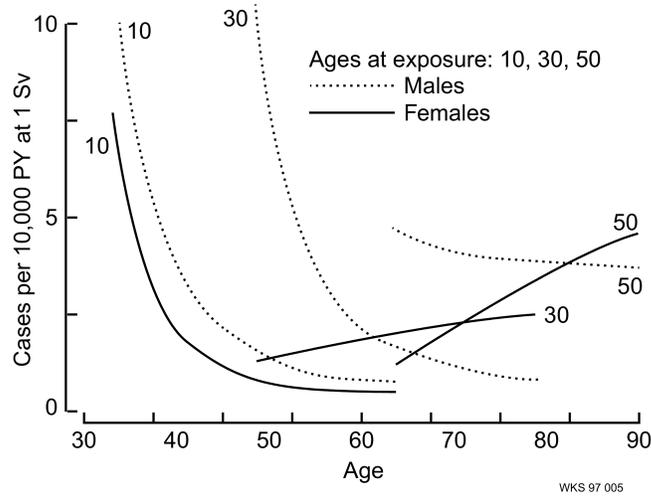


(b) Solid cancers: excess absolute risk per sievert

**Figure 4-3.** Excess relative risk per sievert (a) and excess absolute risk per sievert (b) versus attained age for mortality from solid tumors ([Pierce et al.](#) 1996a).

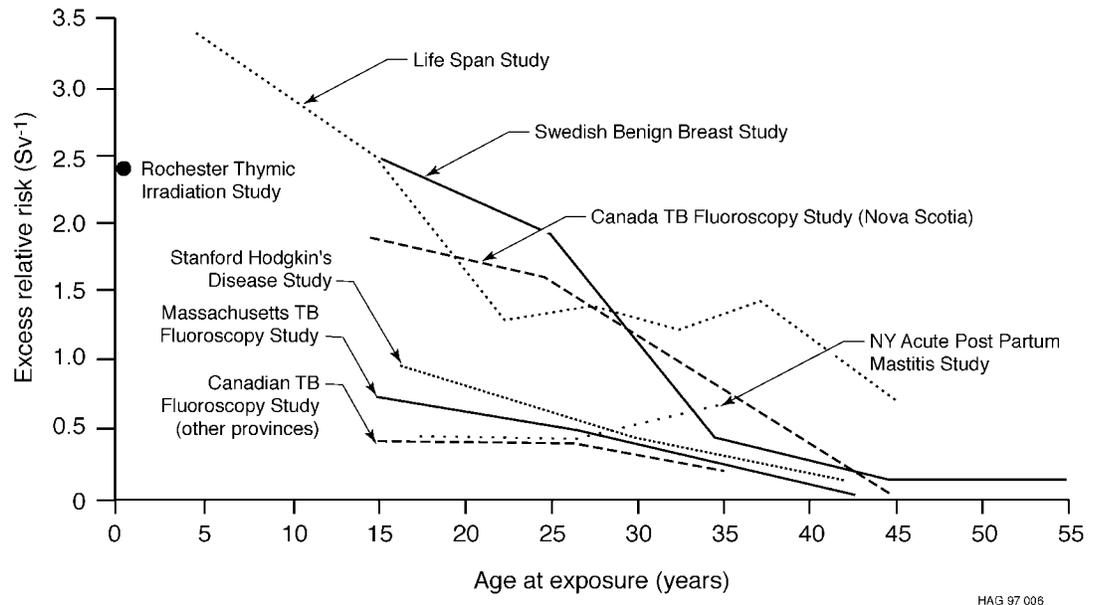


(a) Leukemia: excess relative risk at 1 Sv



(b) Leukemia: excess absolute risk at 1 Sv

**Figure 4-4.** Excess relative risk at 1 Sv (a) and excess absolute risk at 1 Sv (b) versus attained age for mortality from leukemia (Pierce et al. 1996a).



**Figure 4-5.** Excess relative risk per sievert for the incidence of breast cancer in relation to age at exposure ([UNSCEAR 1994](#)).

[Table 4-3](#) shows the average value of the lifetime risk for those under 20 is about 18%  $\text{Sv}^{-1}$ , and for those 20–64 it is about 9%  $\text{Sv}^{-1}$ . These are risks of fatal cancer from radiation exposure at high dose rate and consider all solid tumors together, i.e., not divided by a DDREF. Those under 20 have a lifetime risk about twice that of adults. A risk estimate of twice the average value (2.5 times the adult value) is recommended for the fetus by NCRP ([NCRP 1993a](#)), and the fetus is considered to have risks similar to infants and the young. A factor of about 2 difference between those under 20 and those over 20 is also implied by ICRP, which recommended 5%  $\text{Sv}^{-1}$  for a population of all ages and 4%  $\text{Sv}^{-1}$  for an adult worker population. [A simple algebraic calculation indicates that if the adult ages extend to 68, the lifetime risk for those at 0–18 =  $(0-68) \times 5\% \text{ Sv}^{-1} - (18-68) \times 4\% \text{ Sv}^{-1} = 7.8\% \text{ Sv}^{-1}$ , i.e., those under 18 have approximately twice the adult risk of 4%  $\text{Sv}^{-1}$ .]

Thus, for all cancers taken together a simple and well-justified age correction would be to consider those exposed at ages 0–20 to be twice as sensitive as those exposed as adults. For cancer in some individual organs, the age dependency is similar to that for all cancers. In some it is greater, e.g., about 3 times for female breast tumors ([UNSCEAR 1994](#)) and 6–10 times for thyroid ([UNSCEAR 1994](#); [Ron et al. 1995](#)) for those under 20 years versus those over 20 years. For other cancers specific information is less available and judgments need to be made. In some cases it is not unreasonable to assume first that the age response is the same as that for all cancers and take the risk for those under 20 to be twice the adult risk. The decision to apply age-dependent factors is aimed at reducing uncertainty in the risk estimates in specific cases where the age at exposure is known, or presumed, as in a particular exposure scenario.

**Table 4-3. Lifetime Risk (Mortality) for Solid Tumors versus Age at Exposure for Constant Relative Risk after an Exposure of 1 Sv (Acute, Whole Body) <sup>a</sup>**

Age at exposure	Lifetime risk (%)
Newborn	24.9
5	20.6
10	17.0
15	14.2
20	12.1
25	10.5
30	9.3
35	8.4
40	7.8
45	7.4
50	7.0
55	6.7
60	6.4
65	4.1
70	2.8

<sup>a</sup> [UNSCEAR](#) (1994), Table 30 for a Japanese population of 1985 using constant relative risk projection.

#### 4.7.1 Lung Cancer

The available evidence for lung cancer following exposure to low-LET radiation seems to describe a pattern quite different from that of all cancers taken together. First it is useful to note that in [Land and Sinclair](#) (1991, Table 9) there is little difference in the percentage weights of lung cancer in the three age groups 0–19, 20–64, and 65–90 (19, 13, and 16%, respectively), which implies that the frequency of lung cancer is about the same fraction of the total risk in each age group. Therefore, lung cancer would appear to have an age pattern similar to all cancers. Later information from the LSS shows a different picture. In an extensive discussion of the incidence of attributable lung cancers in the LSS, [Thompson et al.](#) (1994) finds little dependence on age of exposure for lung cancers overall. For one histological type, squamous cell carcinoma, the risk is even found to increase with increasing age at exposure.

Following this evaluation of the incidence data, [UNSCEAR](#) (1994) (Annex A Table 8, part V) gives an absolute risk over the observation period for those less than 20 years old that is many times less than the risk for those over age 20. The BEIR V Committee ([NAS/NRC](#) 1990) used a model that showed a similar difference. Even allowing for a much longer period of expression for the younger ages, this implies a lifetime risk for young ages less than that at older ages. In the most recent LSS report ([Pierce et al.](#) 1996a) this conclusion is reinforced. The authors found that risks decreased with increasing age at exposure for breast tumors and for all cancers, but they increased with increasing age at exposure for lung tumors. The impact of this on the age dependence of the lifetime risk is less certain.

The recent evidence from the LSS is not contradicted by the age at exposure evaluations of lung cancer from radon exposure (see [Chapter 7, Section 7.1](#)). In the BEIR IV Committee

evaluation ([NAS/NRC](#) 1988, p. 49) and the more recent ICRP evaluation ([ICRP](#) 1993b, p. 12) no distinction between the risks for children and for adults is made. The most comprehensive recent evaluation of 11 studies of miners ([Lubin et al.](#) 1994) also found no clear relationship between age at first exposure and risk. This conclusion was reached despite the fact that in the Chinese study 75% of the fatal cancers resulted from those exposed initially at ages less than 20 years.

It must be emphasized that information and data on radiation induced lung cancer in young persons are scant for both low-LET and high-LET radiations. Nevertheless, on the basis of current information, it seems appropriate to consider lung as an exception among the organs, with either very little effect of age at exposure on the lifetime risk or an age response that leans toward higher risk at older ages. In the case of plutonium exposure and lung cancer, it seems inappropriate to apply an adjustment to the risk in favor of greater risks in the young. No correction on the basis of age at exposure is made. However, there is uncertainty because of this which amounts to a factor of two in either direction, that is the risk to those under 20 years age at exposure can range from half the risk to those 20 years and older at exposure to 2 times the adult risk to those 20 years and older at exposure. See [Table 4-5](#) (page 4-19) for a summary of the adjustments to the population lifetime cancer risk estimate distribution to account for uncertainties related to age at exposure.

#### 4.7.2 Liver Cancer

For liver cancer there seems to be no reason to suppose the age dependence for low-LET radiation differs from that of all cancers. For example, in BEIR V, which was derived from the LSS, liver cancer is part of a group of digestive tract cancers in which the risk declines with age at exposure ([NAS/NRC](#) 1990). In the incidence data from the LSS, the [UNSCEAR](#) report (1994, Annex A, Table 8, Part IV) gives the absolute risk over the observation period for those under age 20 as twice that of those over age 20. For the lifetime risk the difference will be greater. For mortality the observed risk is a little less for the young but given the longer expression time for the younger people, the lifetime risk for low-LET radiation can be expected to be greater for those under 20 compared with those over 20.

For the alpha radiation from Thorotrast, neither the Danish study ([Andersson et al.](#) 1994) nor the German study ([Van Kaick et al.](#) 1989) show a clear effect of age at injection. However, in the Danish study the average age of those diagnosed with liver tumors (26.4 years) was less than the average age (31.8 years) of those injected, implying a possibly greater effect on the young. In neither study were large numbers of young people injected and available for comparison. Further discussion on these and other issues relative to exposure from high LET radionuclides is to be found in a symposium proceeding edited by [Van Kaick et al.](#) (1995).

Even though the effects of high-LET radiation are known to be less dependent on modifying factors such as dose rate or oxygen tension than for low-LET radiation, and may similarly be less dependent on age, for liver it seems reasonable to apply an adjustment factor of 2 times the median adult risk for those under 20. However, the uncertainty is large and for those under 20 it is taken to range from the adult risk to three times the adult risk ([Table 4-5](#)).

### 4.7.3 Bone Cancer

[UNSCEAR](#) 1994 (Annex A, Table 8, Part VI) gives an observed risk from the LSS (for low-LET radiation) for both incidence and mortality of 3 times for those under 20 versus those over 20; therefore, an even larger ratio could be expected for the lifetime risk.

For high-LET radiation the principal information comes from exposure to the alpha particles of injected  $^{224}\text{Ra}$  for the treatment of bone tuberculosis and ankylosing spondylitis. In one of the earliest analyses of the bone sarcomas induced by this radionuclide ([Spiess and Mays](#) 1970 and see also BEIR IV, [[NAS/NRC](#) 1988, p. 207]), juveniles and adults were analyzed separately. Juveniles were found to have twice the risk of adults. In many subsequent analyses juveniles and adults were merged together, but in a later analysis documented in [Mays and Spiess](#) (1983), they were once again separated. Mays and Spiess found the risk for juveniles to be 1.4 times those of the adults (see Figure 4-6, BEIR IV [[NAS/NRC](#) 1988]), but BEIR IV comments that if dose protraction were taken into account in the lifetable analysis the difference between juveniles and adults would vanish. In yet another analysis that corrects for competing risks using a proportional hazards model ([Chmelevsky et al.](#) 1986), juveniles and adults were separated into different dose groups. Now, no difference was found for juveniles or adults (see Figure 4-7, BEIR IV [[NAS/NRC](#) 1988]). The BEIR IV Committee concludes that most, if not all, of the former differences between juveniles and adults were due to failure to take into account competing risk, loss to follow-up, and dose protraction.

In the case of radium dial painters, the victims were all young women and the age range was not broad enough to make any conclusion about an age dependence of bone tumor induction. Also because of the very long retention time of  $^{226}\text{Ra}$  in the body, it is difficult to attribute a specific tumor incidence to the dose.

The  $^{224}\text{Ra}$  exposures described above are likely to be the best source of comparison for  $^{239}\text{Pu}$  in bone because they both expose the endosteal cells of the bone and these show little age effect. Nonetheless, with the low-LET exposures showing greater than 3 times the effect for young versus old, it seems reasonable to apply a modest factor of 2 to the median adult risk value to obtain the median risk in those under 20. The uncertainty in the age adjustment is even larger than in the case for liver and is taken to range from equal to the adult risk to 4 times the adult risk ([Table 4-5](#)).

### 4.7.4 Leukemia (Bone Marrow)

The age pattern for the excess absolute risk of leukemia after low-LET radiation exposure of bone marrow (see [Figure 4-4b](#)) is well known and different from some other cancers because it is broadly U shaped. The sensitivity is high in the young, about 3 times that of the young adult and in the old it is about 1.5–2 times that in the young adult. [UNSCEAR](#) 1994 (Annex A, Table 8, Part XII) gives an observed risk (over the whole period of expression) of about 0.75 times for those under age 20 versus those over age 20.

For high-LET radiation the most important source of data on radiation-induced leukemia is from persons who were injected with Thorotrast (e.g., [Andersson et al.](#) 1993). The types of leukemia generated differ somewhat from the distribution of leukemias after low-LET irradiation, e.g., there are more erythro-leukemias and there are more induced cases of Hodgkins lymphoma. The authors did not find any dependence on age at injection among the cases induced. Note that although liver tumors are induced in greater number (5 times or more), the

risk coefficient for leukemia is actually higher because the dose to the bone marrow is much lower than to the liver.

In view of these sources of information, no age correction is applied to the risk of leukemia induced by plutonium irradiation of the bone marrow. However, the uncertainty associated with this absence of age adjustment is taken to be a factor of 1.5 in either direction, that is the risk to those under 20 years age at exposure can range from 0.7 times the risk to those 20 years and older at exposure to 1.5 times the adult risk to those 20 years and older at exposure. See [Table 4-5](#) for a summary of the adjustments to the population lifetime cancer risk estimate distribution to account for uncertainties related to age at exposure.

#### 4.8 Gender Dependence of Risk

In providing the age response data for low-LET radiation given in [Table 4-3](#), [UNSCEAR \(1994\)](#) did not distinguish between gender. Nevertheless, there are some differences in the lifetime risks for males and females, for some organs and tissues. These risks can be seen in [Table 4-4](#), also taken from [UNSCEAR \(1994, Table 32\)](#). In the following sections the differences for the organs of primary interest as a result of plutonium exposure (lung, liver, bone, and bone marrow) are discussed.

**Table 4-4. Site-specific Lifetime Risks for Solid Tumors and Leukemia Following a Whole-body Acute Exposure of 1 Sv<sup>a</sup> ([UNSCEAR 1994, Table 32](#))**

Site of cancer	Risk of exposure-induced death (REID) (%)		
	Males	Females	Both
Leukemia <sup>b</sup>	1.3	0.9	1.1
Esophagus	0.3	0.7	0.5
Stomach	0.9	2.0	1.4
Colon	0.5	0.6	0.6
Liver	2.2	0.3	1.2
Bladder	0.4	0.2	0.3
Lung	1.8	3.1	2.5
Breast	–	2.0	1.0
Ovary	–	0.5	0.3
Other	4.3	2.0	3.1
Total (except leukemia) <sup>c</sup>	10.4	11.4	10.9
Total	11.7	12.3	12.0

<sup>a</sup> Projections are based on age-at-exposure-specific values computed using death rates for Japan in 1985 [[Japan Ministry of Health & Welfare 1985](#)]. Rates were averaged over age at exposure using the population of Japan in 1985.

<sup>b</sup> Leukemia risks were computed using the excess absolute risk model presented in ([Preston et al. 1994](#)). This model has a nonlinear dose response and the risk varies with time, gender, and age at exposure. Projection beyond the current follow-up was based on this model.

<sup>c</sup> Solid tumor risks were computed using linear dose-response models with age-at-exposure and gender-specific relative risks and a 10-year latency period.

### 4.8.1 Lung

For lung, males and females differ by less than a factor of 2: lifetime risk  $1.8 \text{ Sv}^{-1}$  (males) versus  $3.1 \text{ Sv}^{-1}$  (females). In the most recent report ([Pierce et al. 1996a](#)), absolute risk coefficients over the observation period differ only slightly and not significantly: 1.61 (95% CI = 0.29–3.16) per  $10^4 \text{ PYSv}$  for males versus 1.79 (95% CI = 0.88–2.85) per  $10^4 \text{ PYSv}$  for females. Furthermore, the difference in the lifetime risks after 1 Sv for age 30 at exposure is only a little greater for females: 1.6% for males versus 1.9% for females ([Pierce et al. 1996a](#)). Thus limited evidence for an absence of differences due to gender for lung cancer induced by alpha particles from radon progeny suggests at most minor differences ([NAS/NRC 1988](#); [ICRP 1993b](#); Lubin et al. [1995](#), [1994](#)). Consequently, no adjustment for gender is applied to the risk of lung cancer induced by plutonium. However, the uncertainty introduced is a factor of 2 in either direction ([Table 4-5](#)), i.e., the female risk can range from 0.5 times the male risk to 2 times the male risk, and vice versa.

### 4.8.2 Liver

Liver cancer presents a different problem. For low-LET radiation there is about a factor of 7 ([Table 4-4](#)) difference in gender; the males have the higher risk although there may still be questions about whether these are based completely on primary liver tumors. For high-LET alpha particles (from Thorotrast), the difference between genders regarding induced liver cancer is not at all clear. Only two of the thorotrast series discuss the differences in gender: the German ([Van Kaick et al. 1989](#)) and the Danish ([Andersson et al. 1994](#)), both with large numbers of liver cancers. [UNSCEAR \(1994\)](#) notes that in the German series the cumulative rate of liver cancers in the males was about twice that of the females, while in the Danish series it was about the same in the males and females. Together with the strong evidence of the low-LET difference in gender, it seems reasonable to consider the males as having twice the risk of females. Thus, the median population risk should be multiplied by 1.33 for males and 0.67 for females. But there is a large uncertainty which is taken to range from the male risk being equal to the female risk up to about 8 times the female risk ([Table 4-5](#)).

### 4.8.3 Bone

For bone, the excess absolute risk after low-LET radiation over the observation period for males is about 3 times that of females ([UNSCEAR 1994](#), Table 8, part VI) for both incidence and mortality. More recent data from the LSS ([Pierce et al. 1996a](#)) suggest a ratio of 0.12/0.05 or 2.4. In view of the fact that the period of expression in females is longer than in males, the induced lifetime risk will be somewhat less different, perhaps about a factor of 2. For high-LET exposures ( $^{224}\text{Ra}$ ) the data are less specific and show little dependence on the gender of the exposed person. In view of the relatively high risk ratio for males after low-LET radiation, an adjustment factor for males of 1.33 times the median population risk and for females 0.67 times the median population risk is recommended. The uncertainty is such that the male risk could range from being equal to the female risk up to 4 times the female risk ([Table 4-5](#)).

#### 4.8.4 Bone Marrow (Leukemia)

In the case of the bone marrow, the lifetime risks for leukemia in males after low-LET radiation, 1.3% Sv<sup>-1</sup> (UNSCEAR 1994), is only 1.4 times that for females, 0.9% Sv<sup>-1</sup>, and about the same in the latest report on the LSS (Pierce et al. 1996a). For high-LET radiation no difference with gender was observed in the induction of leukemia by Thorotrast. Given the uncertainties involved in these estimates it is not considered appropriate to apply an adjustment factor for gender to the leukemia risk estimates. The uncertainty in the population lifetime cancer risk estimate distribution due to gender differences is taken to be a factor of 1.5 in either direction, i.e., the female risk can range from 0.7 times the male risk to 1.5 times the male risk, and vice versa. Table 4-5 summarizes the adjustments to the median population-average lifetime risk estimates (R) to account for uncertainties related to gender.

**Table 4-5. Summary of Adjustments<sup>a</sup> for Age at Exposure and Gender Applied to the Population Lifetime Cancer Risk Estimate Distribution**

Cancer site	Age at exposure <sup>b</sup>		Gender <sup>c</sup>	
	Under 20	20 and over	Male	Female
Lung	R (0.59R–1.5R)	R (0.77R–1.2R)	R (0.67R–1.3R)	R (0.67R–1.3R)
Liver	1.5R (R–1.9R)	0.77R (0.63R–R)	1.3R (R–1.8R)	0.67R (0.22R–R)
Bone	1.5R (R–2.1R)	0.77R (0.53R–R)	1.3R (R–1.6R)	0.67R (0.4R–R)
Bone marrow	R (0.74R–1.3R)	R (0.87R–1.1R)	R (0.8R–1.2R)	R (0.8R–1.2R)

<sup>a</sup> R = median population lifetime risk estimate. Values in parentheses indicate 2.5 and 97.5 percentiles of distribution of adjustment uncertainties.

<sup>b</sup> Based on the Colorado population where 30% of the total population is under 20 and 70% is 20 and over.

<sup>c</sup> The population consists of equal numbers of males and females.

#### 4.9 Studies of Radiation Workers

In recent years a number of epidemiological studies of the health of workers exposed to low doses of ionizing radiation, often over long intervals, have been reported. Although, in general, such studies suffer from the number of workers and the doses to which they are exposed being too small to contribute directly to risk estimation, they often can provide a range which may help decide whether other risk estimates are substantially in error.

Occupational studies have some advantages, the population is well defined and exposures are usually known from individual monitoring. They may be confounded, however, by internal exposures versus external exposures and by other chemical exposures. In general, control groups must be within the population itself because otherwise the healthy worker effect – the tendency

for working populations to have lower rates of mortality than those of the general population – would make comparisons difficult.

The BEIR V Committee (NAS/NRC) discusses some of the results of 8 occupational studies prior to 1990 which did not yield specific risk estimates but also did not find that estimates of risk of total cancer or leukemia were in error.

Controversy has continued over some of the early studies such as those of the Hanford workers ([Gilbert et al. 1993b](#); [Kneale and Stewart 1995](#); [Gilbert et al. 1994](#)) but more recently, i.e., since 1990, some epidemiological studies of workers have emerged that provide risk estimates, albeit with very broad confidence intervals. Among these are those discussed in [UNSCEAR 1994](#).

#### 4.9.1 [UNSCEAR 1994](#) on Studies of Workers

The importance of low dose worker studies is emphasized in the [UNSCEAR 1994](#) report in which a number of new studies in the UK, Russia and internationally by IARC (see [Glossary](#)) are considered. In spite of broad intervals, these studies give support for risk estimates from the LSS to within a factor of 2 or so for leukemia, lung cancer (Russia) and all cancer. An example is given in Table 4-6 for nuclear workers in the UK and US compared with the atomic bomb survivors ([UNSCEAR 1994](#)) for leukemia and all cancers only. Other examples are provided in Tables 33-40 of [UNSCEAR 1994](#).

**Table 4-6. Comparison of Risk Estimates for Mortality in Survivors of Atomic Bombings in Japan and Nuclear Workers in the U.K. and U.S.**  
([UNSCEAR 1994](#), Table 36)

Group	Size of cohorts	Person-years	Collective dose (man Sv)	Average dose (mSv)	Excess relative risk (Sv <sup>-1</sup> ) <sup>a</sup>		Lifetime risk (% Sv <sup>-1</sup> ) <sup>a</sup>	
					All cancer	Leukemia	All cancer	Leukemia
Survivors of atomic bombings	75,991	2,185,000	10,500	251	0.39 (0.32–0.46)	5.2 (3.8–7.1)	4 <sup>b</sup> (3–5)	0.4 <sup>b</sup> (0.3–0.55)
Nuclear workers in the United Kingdom	95,217	1,218,000	3,198	34	0.47 (-0.12–1.20)	4.3 (0.40–13.6)	10 (<0–26)	0.76 (0.07–2.4)
Nuclear workers in the United States	35,933	705,000	1,140	32	-0.99 (-1.6–0.38)	<1.5 (<-1.5–3.4)	<0 (<0–8.2)	<0 (<0–0.60)

<sup>a</sup> 90% CI in parentheses.  
<sup>b</sup> Based on ICRP with low-dose-rate reduction factor of 2.

#### 4.9.2 Studies of Workers Exposed to Low Doses Since the Report [UNSCEAR 1994](#)

One of the principal developments since the [UNSCEAR 1994](#) report has been the results of the combined analysis of 95,673 workers in the nuclear industry of the U.K., U.S.A. or Canada ([Cardis et al. 1995](#)) which has also been summarized by [Gilbert](#) (1997) from whom [Table 4-7](#) was derived.

It should be noted that although the Excess Relative Risk (*ERR*) for all cancers is slightly negative the upper confidence interval is 0.3, higher than the linear model estimate of 0.18 based on the atomic bomb survivors. The *ERR* for leukemia, 2.2, is well within the linear estimate of 3.7 and the linear quadratic estimate of 1.4, from the atomic bomb survivors. In spite of the broad

ranges involved these results indicate that it is unlikely that linear extrapolation from studies of persons exposed at high doses and dose rates has seriously underestimated risks (Gilbert 1997). Another study of workers in Russia directly on plutonium exposures is described in Chapter 5 of this report.

#### 4.9.3 Studies of Chernobyl Emergency Workers

Very recently some new information has been emerging on the effects of exposure on emergency workers (called by the Russians “liquidators”) at the Chernobyl nuclear plant after the accident in 1986. According to Ivanov et al. (1997a) there are already risks of thyroid cancer identified which are comparable to BEIR V results, excess absolute risk  $EAR/10^4$  PYGy of 1.15 (0.08 – 2.22) versus 1.25 for BEIR V. Another paper of Ivanov et al (1997b) finds leukemia risks, excess absolute risk  $EAR/10^4$  PYGy of 1.31 (0.23 – 23.9) versus 2.61 for the atomic bomb survivors. Yet another paper by the Ivanov group (Ivanov et al. 1998) finds both solid tumors SIR (standardized incidence ratio – see glossary) 1.23 (1.15 – 1.31) and malignant neoplasms of the digestive system in excess, SIR 1.11 (1.01 – 1.24) respectively.

These are preliminary reports of studies that are ongoing and will presumably be updated with longer follow-up, more detailed dosimetry etc., but so far they show reasonable agreement with values expected from the high dose rate exposures of the atomic bomb survivors.

**Table 4-7. Estimates of the Excess Relative Risk (ERR) from International Analyses of Data from Studies of Workers Monitored for External Radiation and from Japanese Atomic Bomb Survivors<sup>a</sup>**

Study population	ERR per Sv (90% CI)	
	All cancers excluding leukemia	Leukemia excluding CLL
International worker study <sup>a</sup>	-0.07 (-0.4, 0.3)	2.2 (0.1, 5.7)
Japanese atomic bomb survivors <sup>b</sup>	0.18 (0.05, 0.34)	0.37 (2.0, 6.5)
Linear model		
Linear term of linear-quadratic model	–	1.4 (<0, 6.5)

<sup>a</sup> Adapted from Cardis et al. (1995)  
<sup>b</sup> These estimates and confidence intervals were calculated at IARC, and were based on male survivors exposed between the ages of 20 and 60.

#### 4.9.4 Results of Worker Studies to Date

Some of the larger worker studies (e.g., Kendall et al. 1992; Cardis et al. 1995) are beginning to realize results which, although still with large confidence intervals, can provide significant values for risk estimates for leukemia and indicative values for all solid cancers. These studies have already shown that the results derived from high dose rate studies such as the atomic bomb survivors are probably not underestimates and probably not serious overestimates either. Results of Russian studies fall into the same general range of risk estimates. Although it is too early to call these studies definitive and, for example, to specify from them a DDREF for converting high dose rate exposure to low dose rate exposures, the continued follow-up and

results from these studies in the future should eventually provide more specific risk estimates to compare with those derived from high dose rate studies.

In the specific case of plutonium workers the results of Russian studies on lung cancer induction (described in [Chapter 5](#)) are within about a factor of two of those expected from the atomic bomb survivors and this must be regarded at this stage, as reasonable agreement.

#### **4.10 Studies That Do Not Agree with “Conventional” Risk Estimates**

A general consensus exists among evaluation bodies about the magnitude of the risks of radiation-induced cancer from the LSS and many other (mainly medical) studies (UNSCEAR [1988](#), [1994](#); [NAS/NRC](#) 1990; [ICRP](#) 1991; and [NCRP](#) 1993b). However, it is also well recognized by these bodies that many uncertainties exist in risk estimates. Risk estimates different from these consensus values have been proposed from time to time by some workers in the field. Some propose or claim much higher risks, others much lower risks. Some of these nonconventional evaluations are discussed in this section, using as far as possible, comments from already published sources.

The UNSCEAR reports have generally not addressed critically the subject of studies that the Committee felt had flaws that resulted in either unusually high or unusually low risk estimates. They have simply not used studies they did not think reached the appropriate standards for inclusion. Recent BEIR committee reports have offered some critiques of these papers, however. The BEIR III report, in particular, considered a number of such reports ([NAS/NRC](#) 1980). Some of the studies involved have been updated in more recent evaluations.

##### **4.10.1 Critiques in the BEIR III Report ([NAS/NRC](#) 1980)**

[Mancuso et al.](#) (1977) and [Kneale et al.](#) (1978) estimated much higher risks for exposed Hanford workers than those found in the LSS: notably 8 per gray ( $8 \times 10^{-2} \text{ rad}^{-1}$ ) for all cancer and higher risks for some individual tumors. [Marks et al.](#) (1978), [Gilbert and Marks](#) (1979), and [Hutchison et al.](#) (1979), analyzing essentially the same data and work force, did not find an excess for all cancers or for most individual tumors. But for two diseases, pancreatic cancer and multiple myeloma they estimated very high risks. The estimates were so high as to be impossible because if they were valid, natural background radiation would then give rise to very high natural rates of these diseases that are not found in the general U.S. population. The BEIR III Committee considered the high estimates of [Mancuso et al.](#) and [Kneale et al.](#) to be the result of low statistical power and chance ([NAS/NRC](#) 1980). Later evaluations of the Hanford workers appear to support this and indeed these later studies show little evidence of radiation effects. But, since broad confidence intervals are involved, the range of results includes risk estimates such as those used by ICRP as well as subzero risk estimates ([Gilbert et al.](#) 1993b).

The BEIR III report also included discussion on the claims of Bross ([Bross](#) 1977; [Bross et al.](#) 1979) that the Hanford analyses of [Mancuso et al.](#) and his own tristate leukemia survey (Bross and Natarajan [1972](#), [1974](#)) indicate that extrapolation to low dose from doses above 1 Gy (100 rads) (as in the LSS at the time) underestimated the risks from doses of about 0.01 Gy (1 rad) by an order of magnitude. The Committee found the statistical methods used by Bross both unpublished and inappropriate. They concluded that his work provided no evidence that the risk of cancer from low dose radiation is greater than that estimated by conventional methods. More recent reports of the LSS have reduced the range of extrapolation to well below 1 Gy (100

rads)—first to 0.2 Gy (20 rads) ([Shimizu et al.](#) 1988) and then to 0.05 Gy (5 rads) ([Pierce et al.](#) 1996a). The response of solid tumors in the LSS is essentially linear down to these levels.

Also discussed in the BEIR III report was a report by [Najarian and Colton](#) (1978) which addressed high leukemia risks in nuclear workers at naval shipyards. It concluded that due to response bias in collecting the data, the analysis was flawed and the report contributed little to our understanding of the risks from low-level radiation. A reevaluation of the shipyard workers in question failed to show a high risk of leukemia ([Rinsky et al.](#) 1981).

Work by Sternglass (presented to the BEIR III Committee) purported to show an increase in infant mortality in the eastern U.S. due to Chinese nuclear testing and claimed support for greater effects of low dose radiation because of work by Petkau et al. ([1975](#), [1976](#)). The Committee concluded, in several pages of discussion, that the available data were not adequate to determine the role of radiation damage in membranes (i.e., the work of Petkau et al. [1975](#), [1976](#)) in relation to radiation-induced pathology in humans. With regard to this and various other radiobiological phenomena, the Committee considered additional studies were needed before interpretation was possible. However, the BEIR III Committee did not believe there was clear evidence of increased infant mortality rates and, thus, they did not believe the allegation of higher risks was substantiated.

The Committee also examined reports relating to cancer and natural background radiation including those by [Frigerio and Stowe](#) (1976) that found an inverse correlation between background rates at different altitudes and all cancers as well as for some individual cancers. This finding was explained subsequently ([Weinberg et al.](#) 1987) when the effect of altitude was taken into account. [Jacobson et al.](#) (1976) did not find an association between leukemia and background levels. [Eckhoff et al.](#) (1974) found an increase in leukemia with background up to altitude 2000 ft and a decrease thereafter. [Archer](#) (1978) took into account geomagnetic variation as well as altitude and found a positive correlation between the two variables and cancer. He estimated that 40–50% of all cancer might be due to background radiation. The BEIR III Committee concluded that such studies, aggregating cancer mortality data crudely by geographical region, do not constitute a basis for associating cancer rates with background radiation. This approach was not considered fruitful.

#### **4.10.2 Comment in the BEIR V Report**

In the BEIR V report ([NAS/NRC](#) 1990), the Committee, rather than criticizing papers with unconventional risk results individually, provided a chapter entitled Low Dose Epidemiological Studies in general. The Committee considered reports of adult onset myeloid leukemia after diagnostic radiology, an issue still unresolved. It considered fallout from nuclear weapons testing in Nevada and Utah. It found the [Johnson](#) (1984) study reporting high risk estimates weak in its reliance on volunteers to collect the data. However, the [Machado et al.](#) (1987) study on Utah fallout found excesses in leukemia only especially in childhood but at rates not inconsistent with other results. Also considered were reports on weapons test participants indicating either chance phenomena or doubtful controls. It was concluded that cancer among individuals near nuclear installations was unlikely to be the result of radiation exposure.

The Committee also considered a number of studies of high background radiation areas and noted that an increase in chromosome aberration frequency is observed frequently but no significant increase or decrease in frequency of cancer has been found.

### 4.10.3 Interaction with Dr. Alice Stewart

The risk estimates that Dr. Alice Stewart and her colleagues have produced on studies like those on the Hanford workers ([Mancuso et al. 1977](#); [Kneale et al. 1978](#)) are substantially higher than those used in this report (see [4.11](#)). Dr. Stewart has also made comments about selection bias in the atomic bomb survivor study ([Stewart and Kneale, 1990](#)) (see later [6.3.1.3](#)). In view of this, Dr. Alice Stewart was invited to attend a meeting of the HAP and present her methods to the Panel. She attended the Panel on March 4, 1997 and discussed the early Oxford Survey studies of x-ray induced childhood cancers which, while at first disputed, have recently been accepted as one of the studies with the lowest significant excess risk at 10 mGy ([Doll and Wakeford 1997](#)). More of her time was spent on the studies of the Hanford workers made by George Kneale and herself. She presented results showing significant and substantial excesses for certain specific cancers that implied high risks for these cancers. In their papers a dependence on age at exposure was claimed by these authors that showed older persons at much greater risk than younger persons, a result not usually found by others. The methodology for arriving at these results (which she attributed to her colleague George Kneale) did not emerge clearly. Questions from members of the panel did not result in sufficient clarification of the methodology to enable RAC or HAP to extrapolate Stewart and Kneale's work to the Rocky Flats historical risk study. As a result a spokesman for the panel wrote to Dr. Stewart requesting her assessment of the risk in the case of certain exposures to plutonium. She supplied a new reference on recent results of the worker studies but stated that she did not think these could be applied in the case of alpha emitters like plutonium. Consequently, the interaction with Dr. Stewart did not result in alternative risk estimates for the plutonium exposure situations at Rocky Flats.

### 4.11 Dose Response for Cancer Induction in the Low Dose Region

Radiation effects are both deterministic and stochastic. Deterministic effects by definition have clear thresholds above which the severity of the effect increases with the dose. Stochastic effects occur randomly and affect relatively few members of an exposed population. The severity is not usually considered to be related to dose. Cancer is the principal stochastic effect. Well documented dose responses, linear or linear quadratic, are known for cancer at moderate to higher doses. In many human studies these responses persist to low doses: to 0.05 Gy in the LSS ([Pierce et al. 1996a](#)); to 0.02 Gy for chromosome aberrations in human lymphocytes ([Lloyd et al. 1992](#)); and to even lower doses (e.g., to 2.5 mGy of x-rays and 0.1 mGy of neutrons) for some radiobiological endpoints in laboratory systems ([Sinclair 1993b](#)). A significant excess of leukemia was detected among British atomic energy workers exposed to doses up to 400 mSv with an average dose of about 34 mSv (3.4 rads) ([Kendall et al. 1992](#)), but this excess was not found in a smaller U.S. group with about the same average exposure ([Gilbert et al. 1989b](#)) ([Table 4-7](#)). It was found, however, in the International Association for Research on Cancer (IARC) study which included many of the British workers ([Cardis et al. 1995](#)). Recently a review of studies on the risk of childhood cancer following fetal x-irradiation was undertaken. Four of eleven studies showed a significant relative risk. The pooled data also showed a significant relative risk whether or not the largest study, the Oxford Study of Childhood Cancer, was included. The authors concluded that an increase in risk is caused by doses of 0.01 Gy and the excess risk is of the order of 6% Gy<sup>-1</sup> ([Doll and Wakeford 1997](#)). This conclusion was further

reinforced subsequently in a more general review of low dose responses by one of these authors ([Doll](#) 1998).

An absence of a demonstrable effect in low dose circumstances where statistically it could not be expected to be detected does not prove that the effect is not there. It is not evidence of a threshold. In some areas of radiobiology (especially with alpha emitters) the term "practical threshold" ([Evans](#) 1974) has been used to describe the apparent absence of effects in the low dose region although this term is not without its critics.

Human beings have been exposed to alpha emitters in a variety of circumstances including short-lived  $^{224}\text{Ra}$  ( $T_{1/2} = 3.66$  days) in medical treatment,  $^{226}\text{Ra}$  inadvertently in dial painting, and radon in mines and homes. Rowland, in summarizing many of these studies, concludes that for radium-induced bone sarcomas "a threshold hypothesis is as good as any other," but for radium (radon)-induced head carcinomas, more positive models involving linear, linear exponential, and dose squared exponential functions fitted the data equally well, probably because the numbers were small ([Rowland](#) 1994).

Animal studies have been interpreted to yield practical thresholds for bone sarcomas induced by  $^{226}\text{Ra}$  in mice of 1.1 Gy, in dogs of 0.5 Gy, and in humans of 0.8 Gy ([Raabe](#) 1983). [Mays](#) (1988) pointed out, however, that in the animal experiments, too few animals were included in the low dose groups to have produced an observable effect. [Raabe](#) (1984) postulated a threshold for plutonium-induced bone sarcoma in dogs of 0.06 Gy. [Mays](#) (1988) finds induced bone cancer cases below this dose level. Opinions clearly differ, even for the responses from alpha particles.

No solid evidence of a threshold after low-LET radiation has been produced although it is evident that at very low doses of a causative agent the existence or nonexistence of an effect is difficult to prove because of statistical considerations.

The Health Physics Society has maintained in a statement made in 1996 ([HPS](#) 1996) that there was no evidence of health effects below 0.1 Sv and that risk estimates should not be made at dose rates below  $0.05 \text{ Sv yr}^{-1}$  ([HPS](#) 1996). However, as indicated in [section 4.11.2](#) there is some evidence of effects in humans below 0.1 Sv and also in laboratory studies.

#### 4.11.1 Biophysical Perspective

It is a widely held assumption that a single molecular change can result eventually in a cancer (whether that change is the result of a single causative event or the unrepaired survivor of many such events that were repaired). On this basis, a linear response, or at least a progressive response with dose of a causative agent such as ionizing radiation, in the low dose region is inherently reasonable. The basic biological unit is the cell and for ionizing radiation effects perhaps it is a smaller sensitive region or sensitive targets (possibly of molecular dimensions) within the cell, that deserves our attention. Depending on the size of the sensitive volume chosen, calculations can be made of the dose that will cause one event or less per sensitive target. Below such a dose, effects could be expected at least initially, to be linear. Such a dose will be very different for x- or gamma rays on the one hand and fast neutrons or alpha particles on the other. An example of such calculations is given in Table 4-8 ([ICRU](#) 1983).

**Table 4-8. Mean Number of Energy Deposition Events,  $\eta$ , in Spheres of 5.6  $\mu\text{m}$  Diameter and Percentage of Affected Volumes for x-rays and Fast Neutrons**

Absorbed dose (mGy)	x-rays <sup>a</sup>			Fast neutrons <sup>b</sup>		
	Equivalent dose (mSv)	$\eta$	Percentage	Equivalent dose (mSv)	$\eta$	Percentage
0.1	0.1	0.01	1.0	1	$3.5 \cdot 10^{-4}$	0.03
1	1	0.10	9.7	10	$3.5 \cdot 10^{-3}$	0.3
10	10	1.02	63.9	100	$3.5 \cdot 10^{-2}$	3.4
100	100	10.2	100.0	1000	$3.5 \cdot 10^{-1}$	29.5

<sup>a</sup> x-rays of 1 mm Cu half value layer. Data taken from [Braby and Ellett](#) (1971).

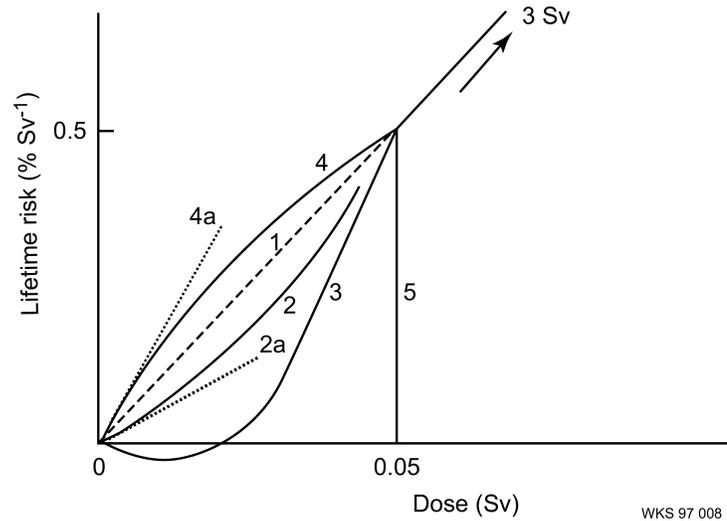
<sup>b</sup> Monoenergetic fast neutrons of 2 MeV. Data taken from [Caswell and Coyne](#) (1976).

For a spherical sensitive volume of 5.6  $\mu\text{m}$  diameter ([ICRU](#) 1983), less than 100% (63.9%) of the cells will be affected (i.e., have an event) at a dose of 10 mGy of x-rays. For fast neutrons at the same absorbed dose, 10 mGy = (100 mSv) in the example, only 3% of the cells will be affected). At doses below these levels proportionally fewer and fewer cells or nuclei will be affected; consequently, the chance of any one of these resulting in a cancer is likely to fall linearly. From these considerations alone the initial response to radiation in tissue should be linear. Later developments in the complex chain of events between this initial response and the expression of a cancer may well distort the form of the dose response, possibly in predictable ways and especially in selected cases. However, the broad form of response at the lowest levels of dose is likely to be a steady increase in frequency with the dose.

#### 4.11.2 Extrapolation to Low Dose From High or Moderate Doses

This section concentrates on the human cancer data in the atomic bomb survivor LSS. It is now apparent that the data for induced solid tumors from the LSS are broadly linear with dose from 3 Sv (organ dose) downward, which demonstrates a significant excess because of exposure at doses as low as 0.05 Sv (5 rem) ([Pierce et al.](#) 1996a) which may be due to a bias (see later). For studies of childhood cancer after fetal irradiation the dose is even lower, a significant excess is shown at 0.01 Gy (1 rad) ([Doll and Wakeford](#) 1997). Since we are presently unable to observe a significant response in the LSS at doses below 0.05 Sv (5 rem), a question of much interest and debate is what happens to the response below 0.05 Sv (5 rem). There are at least five possibilities for extrapolation to lower doses, each of which is represented in [Figure 4-6](#): (1) the response continues in a linear fashion as dose approaches zero, (2) the response reaches zero in sublinear fashion with a slope of about half the linear slope, as dose approaches zero (3) an extreme case of (2) in which the response dips below the line for zero dose effect (hormesis, see [Section 4.11.5](#)); (4) the response reaches zero in a supralinear fashion with a slope of perhaps twice the linear slope as dose approaches zero, and (5) the response drops vertically to zero at a threshold of 0.05 Sv, (5 rem) or lower (see [Figure 4-6](#)).

If one knew nothing about the nature of radiation responses, one would expect curve 1 to apply. The model response is firmly linear in the known dose range so far, so why wouldn't it stay linear? *Only if some other controlling factor enters in at low doses can one expect deviation from linearity.* Other factors do enter in—most notable in radiobiology are dose rate effects discussed in the next section and adaptive responses discussed in [Section 4.11.4](#).



**Figure 4-6.** Possible forms of response (cancer induction) versus dose in the low dose region. Curve 1: linear; curve 2: sublinear, i.e., linear with a DDREF of 2 (i.e., 2a); curve 3: sublinear, with threshold and hormesis; curve 4: supralinear, initial slope 4a; curve 5: threshold at 0.05 Sv. (Sinclair 1998).

#### 4.11.3 Dose Rate Effects

For low-LET gamma radiation, such as that from the atomic bombs, low dose rates are known to be less effective than high dose rates. Experimental studies in animals show factors of 2 to 10 times less for this effect (NCRP 1980; UNSCEAR 1993). In humans, data on dose rate effects are less decisive. For the atomic bomb data itself, which is nominally linear, a factor of 2 is possible, but a much larger factor is not consistent with the statistical limitations. For breast and thyroid a factor of 2 is possible also but linearity is preferred (ICRP 1991). For lung cancer (Howe 1995) there appears to be a larger dose rate factor. Considering all these points, evaluation bodies such as ICRP and NCRP assigned a value of 2 to the DDREF for low-LET radiation, i.e., they chose curve 2 on Figure 4-6 as the most likely response at low doses. To choose a factor for the DDREF other than 1 may not be the most conservative position, but among factors that might be proposed for a DDREF, 2 is relatively conservative and still recognizes the importance of dose rate effects. ICRP outlined their reasons for this choice in publication 60 (ICRP 1991 paragraph B62). In a consideration of uncertainties in the LSS, NCRP included a range of values of the DDREF from 1 to 5 with different frequencies (NCRP 1997b). This actually represents a broad range of models of dose response but does not include the extreme concepts of supralinearity or threshold. For further discussion see Section 6.3.5 in which an allowance for supralinearity is made.

Absence of a dose-rate effect is characteristic of a linear dose response which is often found with alpha particle carcinogenicity in animals especially at low doses (see NCRP 1990, Fig. 7.1 and Fig. 7.2). In the case of some alpha emitters such as radon and inverse dose rate effect

(commonly observed with fission neutrons, [Hill et al.](#) 1984) seems to be evident over part of the dose range but the effect is less evident at low doses ([Lubin et al.](#) 1995). In the particular case of plutonium experiments on lung tumors induced in rats show little or no effect of fractionation, corresponding to a DDREF of 1 ([Sanders and Mahaffey](#) 1981).

#### 4.11.4 Adaptive Responses

An important phenomenon that occurs uniquely at low doses is what has come to be known as adaptive response. The typical expression of an adaptive response is as follows. The response to a given (challenge) dose of radiation (e.g. number of chromosome aberrations induced) is reduced if a small priming dose is given at an appropriate time prior to the challenge dose. One of the most important of these responses has been identified to modify the number of chromosome aberrations induced in human lymphocytes. In this case, the response to doses like 1.5 Gy have been modified by conditioning doses of 0.005 to 0.02 Gy given about 6 hours prior to the challenge dose. The phenomenon has been interpreted to result from the priming dose activating a repair mechanism which reduces the response at a later time. Apparently the range of priming doses is limited, the time for presenting the challenge dose is critical, the challenge dose itself needs to be of a reasonable magnitude and the response has been found to vary greatly between individual donors of the lymphocytes. Nevertheless, the adaptive response has been seen in many other systems including a variety of mouse cells and with some chemical agents such as N-methyl-N-nitro-N-nitrosoguanidine, hydrogen peroxide and bleomycin as well as with radiation. The subject has been reviewed by [UNSCEAR](#) (1994) Annex B. UNSCEAR concluded that there were many examples of this phenomenon and provides some speculation on possible mechanisms. It also concluded that:

the presence of an adaptive response is not readily evident from the results of experiments in mammalian organisms in terms of reduced tumor induction. The low statistical power of epidemiology studies also prevents a clear statement on the presence of an adaptive response in humans exposed to low doses.

It should be noted that if an adaptive response with respect to radiation induced tumors in humans were to exist, and conditions were right for inducing it, the effect would be to reduce the linear slope of a curve such as 2a in [Figure 4-6](#) by some factor which seems unlikely to exceed about a factor of 2.

#### 4.11.5 Hormesis

Hormesis or a hormetic response is one in which an agent normally deleterious at high doses produces a beneficial effect at low doses. Stimulatory effects are sometimes seen in plant systems exposed to low dose radiation, and other evidence of hormetic effects is claimed ([Luckey](#) 1992; [Kondo](#) 1993). If there were to be evidence of hormesis relating to radiation induced cancer a response curve like that of curve 3 in [Figure 4-6](#) would be observed. While some have claimed that an initial point at about 100 mSv for leukemia has been observed to be below the line for zero effect in some analyses of the LSS, other analysts point out that this point includes zero effect in the estimate of statistical uncertainty and, therefore, cannot be considered to be “below the line” of zero effect. Solid tumors in the LSS do not show any such points

nominally or actually “below the line.” Indeed, some evidence of supralinearity is apparent in the latest mortality data ([Pierce et al. 1996a](#)). Hormetic responses with respect to radiation carcinogenesis have not been clearly demonstrated in the low dose region, although statistical difficulties are such that hormetic responses are sometimes claimed.

There are, however, persistent claims of an initial negative response in the low dose region (which some may interpret as hormesis or at least a conflict with the linear no threshold response) in one large ecological study of the effects (lung cancer) of radon and its decay products on people in home environments ([Cohen 1991](#); [Cohen 1995](#); [Cohen 1997](#)). This study, although ecological in nature and therefore subject to many inherent uncertainties, perhaps because of its size and the care with which possible confounders have been examined, has caused much controversy. Explanations offered recently by [Lubin](#) (1998a) and by [Smith et al.](#) (1998) have not been accepted by the author of the study (Cohen [1998a](#), [1998b](#)) although rejoinders have also been published in the same exchange ([Lubin 1998b](#); [Field et al. 1998](#)). In spite of Cohen’s defense of his study it seems unlikely that in the presence of such a large ill defined smoking factor that a true response to low levels of radon can be elicited in such a study however worthy or careful. The results of case control studies in the low dose region do not show this negative response with dose ([Lubin and Boice 1997](#)).

#### 4.11.6 Supralinearity

The response identified by curve 4 is usually known as supralinear, i.e., the slope of the line close to zero is greater than that of the linear model response. A number of investigators espouse this view, for example J. Gofman, cites the LSS itself as evidence of supralinearity ([Gofman 1989a](#)). His analysis has been criticized ([Muirhead and Butland 1989](#); [Piepho 1992](#)), but Gofman ([1989b](#), [1992](#)) has countered the criticisms. [Nussbaum and Köhnlein](#) (1995) also provide some support for this idea. The idea of supralinearity in the LSS data would not seem to be supported by some views of the low dose data which finds a less than linear tendency in the low dose region ([Shimizu et al. 1993](#)). However, the most recent analysis at RERF ([Pierce et al. 1996a](#)) with more data seems to indicate some support for supralinearity in the mortality data below 0.5 Sv. Supralinearity is less evident in the incidence data.

The LSS data will continue to accumulate in the future, and perhaps in time the analyses will become more definitive in the low dose region. At present supralinearity, linearity and sublinearity within a range are all possible given the epidemiological data in the LSS. Without our knowledge of radiobiology a DDREF might be difficult to justify. However, the radiobiological evidence is very strong and convincing to many radiobiologists and bodies like ICRP, NCRP, and UNSCEAR and BEIR committees.

#### 4.11.7 Threshold

Some discussion about threshold in the low dose region has already been provided in the introductory [Section 4.11](#). Ideas about a threshold ([Figure 4-6](#), curve 5, threshold at 0.05 Sv, 5 rem) seem to derive from two sources. The first source is that thresholds are well known for deterministic effects (based mainly on cell killing and direct tissue damage). Consequently, persons who do not distinguish between the very different nature of stochastic and deterministic responses expect thresholds to occur with stochastic effects also. The second source is that in a very low dose region, below where stochastic effects can be shown to be significant, absence of

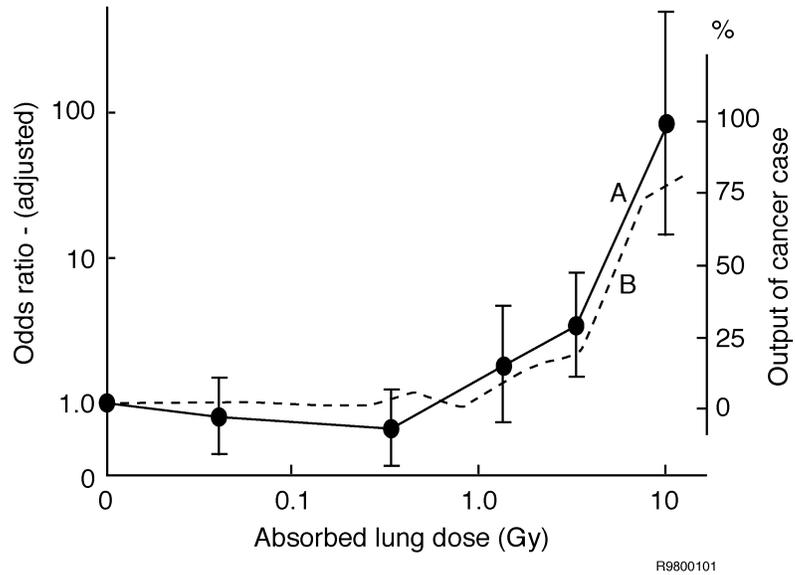
effects or even small negative effects are seized upon as support for a threshold. In fact, statistical uncertainties are such that significant results often cannot be obtained or expected in this region. These statistical difficulties do not mean that effects are not there or will not be there, for example, if a much larger sample of data becomes available. In [Figure 4-6](#), there seems no reason to expect the form of the response for low-LET radiation to decline at once to zero—at 0.05 Sv (5 rem)—or even at lower values.

Nevertheless, there are examples of radiation responses in which a threshold in the response or a quadratic form appears to fit better than linearity. [Rossi and Zaider](#) (1996) recently have suggested that protracted doses of low-LET radiation do not produce lung cancer at doses less than about 2 Gy and they cite some examples from radiotherapy and fluoroscopy. With high-LET radiation the presence of a practical or quasi threshold is even more common, as in the well known case of the radium dial painters ([Rowland](#) 1975). In the particular case of plutonium and lung tumors a case control study of Russian workers at Mayak finds little effect in the low dose region and proposes a threshold of 0.8 Gy ([Tokarskaya et al.](#) 1997). They cite and support the extensive and detailed findings of [Sanders et al.](#) (1988d) on rats exposed to PuO<sub>2</sub> in which again, lung tumors are fit best either with a quadratic, or a threshold at about 0.8 Gy. The human and rat responses are shown in [Figure 4-7](#).

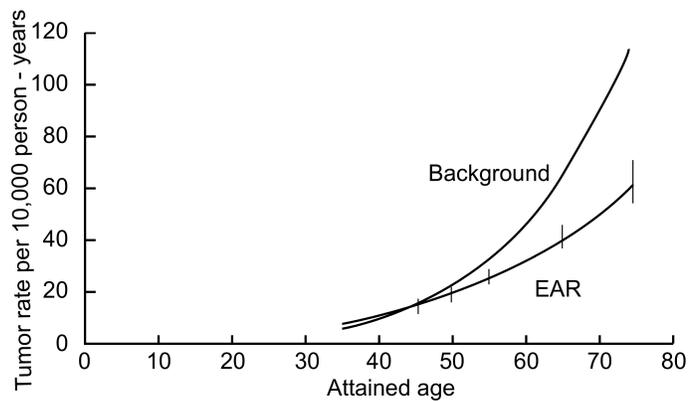
In contrast, in cohort studies of the same Mayak workers in a better defined study population with respect to plutonium exposure, linearity seems to be an excellent fit and in the region of the “threshold” of 0.8 Gy the mortality from lung cancer appears to be about 5 times the natural spontaneous rate (see [Figure 5-2](#)). Given such contradictory examples it is not possible to rule out thresholds or apparent thresholds in some unusual circumstances.

#### **4.11.8 Linearity in the Dose Response for the LSS Application of the Armitage–Doll Model**

In a very recent development Mendelsohn ([1994](#), [1996](#)) has pointed out the similarity between the linear quadratic response of leukemia and chromosome aberrations and the linear response for solid tumors and induced mutations (e.g., glycophorin A). It is also pointed out that the [Armitage and Doll](#) (1954) model predicts a human cancer response with age roughly proportional to the sixth power of the age. This is believed to be the result of cancer developing in perhaps six or seven (say  $n$ ) stages, which is a model supported by some recent findings concerning multistage development in some tumors ([Fearon and Vogelstein](#) 1990). Mendelsohn hypothesizes that radiation, acting as a mutagenic agent, can induce any one of the  $n$  stages of a solid cancer. If this is so, then background cancers not due to radiation must have completed  $n$  stages on their own while radiation induced cancers must have completed  $n-1$  stages on their own and received the other ( $n^{th}$ ) from their radiation exposure. To test this hypothesis, the LSS data were analyzed in detail separating out the radiation-induced cancers from the background not containing these cancers. Both are plotted as a function of attained age ([Figure 4-8](#)).



**Figure 4-7.** Development of lung cancer from  $^{239}\text{Pu}$  inhalation as a function of dose. Comparison of case-control and experimental studies. A. Mayak workers case-control, OR(adjusted) ([Tokarskaya et al. 1997](#)); B. Experimental data for rats, % ([Sanders et al. 1988d](#)).



**Figure 4-8.** Tumor rate versus attained age in background and excess absolute tumors of atomic bomb survivors. The vertical bars represent standard error. The power exponent for the background response is 4.15 and the EAR is 3.03, consistent with the prediction of the model ([Mendelsohn 1996](#)).

The exponent of the power law for the background cancers (4.15) was 1.1 more than that for the radiation-induced cancers (3.03), just about what is expected. This is powerful support for linearity in the dose response for radiation induced cancers over the whole dose range for the instantaneous exposures of the atomic bombs.

#### **4.11.9 Conclusions**

In view of all of these considerations it seems most appropriate to consider that finite risks are the result of low dose exposures. Linearity (with a DDREF applied) in the low dose region may be most appropriate for risk estimation. It is at least as likely to apply as any other form of response and, hopefully, the response chosen with a DDREF of 2 is a good estimate. Uncertainty evaluation suggests the risk estimate determined in this way is within a factor of 2.5 to 3 in either direction ([NCRP 1997b](#)).

## 5. EPIDEMIOLOGICAL STUDIES OF PERSONS EXPOSED TO PLUTONIUM

This chapter and the following three chapters each describe an approach to risk estimation and its uncertainties. The four approaches to risk estimation were outlined in the introduction ([Section 1.7](#)). They include studies of (1) populations exposed directly to plutonium, (2) low-LET exposures in the LSS of the atomic bomb survivors, together with evaluations of alpha RBEs, (3) humans exposed to other alpha emitters, and (4) animal experiments involving plutonium and other alpha emitters. This chapter concerns direct plutonium exposures in humans, i.e. the emphasis is on evaluating risks to human tissues from deposition of plutonium directly.

### 5.1 Introduction

The most direct approach to risk estimation for plutonium induction of cancer in humans would be an epidemiological study on humans exposed to plutonium. However, there are relatively few human experiences with plutonium in Western countries and no studies that have sufficient exposure levels and statistical power to derive risk estimates. Important data of great significance are beginning to emerge from Russian experiences although the data available so far are preliminary and lacking in many important details. Nevertheless these sources appear capable of providing risk estimates directly from plutonium exposures. The plutonium epidemiological studies available up to 1994 were reviewed by [UNSCEAR](#) (1994) and are described in the following section.

### 5.2 Human Plutonium Studies Discussed in [UNSCEAR](#) (1994)

The following is quoted from [UNSCEAR](#) (1994), Annex A. The numbers refer to paragraphs in the report.

315. Animal experiments have shown that plutonium is absorbed by the oral route but slowly dissolved in the alveolar macrophages after inhalation, which means that the highest doses are delivered to the lung.<sup>c</sup> When plutonium isotopes enter the blood they are concentrated in the liver and by various mechanisms at the bone surface [[Vaughan](#) 1986], but their longer half-lives cause many of the alpha emissions to be made after the radionuclides are more widely distributed within the relatively acellular calcified bulk of the bone.

316. In two of the studies of nuclear workers exposed to plutonium a substantial proportion of the radiation workers were monitored for plutonium: for workers at the Sellafield plant [[Smith and Douglas](#) 1986] detailed dose estimates of plutonium are not yet available; for workers at the Rocky Flats plant, individual plutonium body contents were estimated from health physics records based on periodic urine bioassays [[Wilkinson et al.](#) 1987]. The Rocky Flats study included 5,413 white males employed for at least two years, and follow-up was to the end of 1979. The average external dose (low-LET radiation) for the entire cohort was 41 mGy, and the average plutonium

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<sup>c</sup> Note added by authors: This is initially and to soft tissues only. Eventually, the highest doses (about two times higher than lung) are received by the bone surface ([ICRP](#) 1995b).

content of the body was 65 Bq. Mortality was compared with United States national rates for the entire group, and no excess was found for all causes or for all cancers. There were no deaths from bone cancer. When mortality in employees with body burdens greater than 74 Bq was compared with that in employees with smaller body burdens, using lag times of 2, 5 and 10 years, elevated rate ratios were found for all causes of death and for all lymphopietic tumours. For all causes of death these increases were not statistically significant for any of the lag times considered, and for lymphopietic tumours (which included one myeloid leukemia) the increase was significant only for a 5-year lag time. Some other cancer sites also showed elevated rates, but none were significantly elevated. There were no elevated rate ratios for either bone or liver cancer. There is no clear evidence of an effect of plutonium in this study.

317. Twenty-six men who worked with plutonium during the Second World War under very crude conditions at the Los Alamos Laboratory have also been studied [[Voelz et al. 1985](#); [Voelz et al. 1989](#); [Voelz and Lawrence 1991](#)]. Inhalation was the primary mode of plutonium exposure. Current estimates of the systemic plutonium depositions in these individuals range from 52 to 3,180 Bq, with a median value of 500 Bq. The last published follow-up included the period up to 1990. By that time, seven individuals had died. The causes of death were lung cancer (two cases), myocardial infarction, arteriosclerotic heart disease, accidental injury, respiratory failure due to pneumonia/congestive heart failure and osteosarcoma of the sacrum. Three men also reported a history of skin cancer. The man who died from osteosarcoma<sup>d</sup> did not suffer from Paget's disease, which is usually associated with bone sarcoma at older ages. In a separate study, all workers at the plant who had estimated plutonium depositions of 370 Bq or more on 1 January 1974 were identified [[Voelz et al. 1983](#)]. Of the 224 white males in the cohort, 43 had died at the time of the last follow-up compared with 77 expected based on United States national rates; 8 men had died from cancer compared with 15 expected.

318. Workers in a radiochemical plant at Mayak [[Hohryakov and Romanov 1994](#)] received exposures from both external gamma-radiation and plutonium, about one quarter of the total exposure being from the latter. Those in the highest dose group had over 4 Sv total ([Table 39](#))<sup>e</sup>, and a significant excess of lung cancer was noted (see paragraph 237).

Elsewhere in the [UNSCEAR \(1994\)](#) report (under the heading of occupational studies) is a discussion concerning the study of the radiochemical workers at Mayak.

237. In another Russian occupational study, the frequency of lung cancer was investigated among 2,346 workers in the Mayak radiochemical plant who were exposed both externally and internally to plutonium [[Hohryakov and Romanov 1994](#)]. External

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<sup>d</sup> This tumor may have resulted from exposure to plutonium since the spontaneous incidence of osteosarcoma is very low.

<sup>e</sup> Reproduced here as [Table 5-1](#).

exposures were determined by film-badge dosimetry, and lung doses from inhaled plutonium were determined for all individuals using measurements of the excretion of radionuclides in urine and a lung clearance model. The relative biological effectiveness of plutonium alpha particles was taken to be 16. Mortality was studied during 1970-1989, at the end of which time the total collective combined dose to the lung in the group of 2,346 workers was 4,812 Sv. Of that combined dose, 3,327 Sv was from external exposure and 1,485 Sv from inhaled plutonium (RBE for alpha particles = 16). The number of deaths observed and the number expected from national rates in the former Soviet Union are shown in [Table 39<sup>f</sup>](#). The risk of mortality increased with increasing equivalent dose and was significant among workers in the highest dose group. Overall, the relative risk was  $1.8 \text{ Sv}^{-1}$  compared with  $1.63 \text{ Sv}^{-1}$  for the survivors of the atomic bombings, [[Shimizu et al.](#) 1990, Table 4: both sexes]. The authors also compared their estimate of the lifetime risk for lung cancer in these workers,  $0.033 \text{ Sv}^{-1}$ , using an internal control and applying a low-dose-rate reduction factor of 2, with the ICRP-derived value from the survivors of the atomic bombings,  $0.0068 \text{ Sv}^{-1}$  [[ICRP Publication 60](#) 1991]. They pointed out that against national statistics the result would be  $0.014 \text{ Sv}^{-1}$ , closer to the ICRP-derived value. Even better agreement with the ICRP value would have resulted if the low-dose-rate reduction factor had not been applied (equivalent to a reduction factor of 1). It should be noted that a substantial part of the occupational exposure (about 25%) is from plutonium alpha particles, and for these a low-dose-rate reduction factor would not be expected to be applicable. Also, the contribution from the alpha particle portion depends on the value of RBE selected (16 was used). A more complete study of these workers would include information on the smoking habits of the workers, on the possible influence of the healthy worker effect and on the precision of the dosimetry.

**Table 5-1. Lung Cancer Deaths in Workers at the Mayak Radiochemical Plant ([Hohryakov and Romanov](#) 1994), from [Table 39](#) ([UNSCEAR](#) 1994)**

Cumulative equivalent dose in lungs (Sv)	Number of workers	Observed cases	Expected cases
0-0.25	470	0	2.1
0.26-1.00	607	4	6.2
1.01-4.0	929	19	16.2
>4.00	340	22	8.1
All groups	2346	45	32.6

### 5.3 Additional Human Plutonium Studies

The [UNSCEAR](#) (1994) report did not discuss the U.S. National Plutonium Workers Study, which surveys workers at Los Alamos National Laboratory, the Mound Laboratory, and the Rocky Flats Plant. Studies up to 1987 ([Tietjen](#) 1987) have shown that lung cancer in these workers is not only not elevated, but it may even be significantly lower than national averages.

<sup>f</sup> Reproduced here as [Table 5-1](#).

However, the studies did not account for smoking. Consequently, the result for these low exposures, which were given only in terms of plutonium uptake, cannot be considered significant. Dose estimates were not given.

Mention should also be made of another brief Russian paper ([Hohryakov et al. 1994](#)), on population exposures to plutonium. Plutonium burdens were measured in residents of Chelyabinsk (and also in Gomel) and found to be dependent on the length of residence in those locations. For longer-term residents, plutonium burdens were found to be 30 times those in Western Europe; nevertheless, they are still small burdens. A risk estimate based on calculated doses shows that potential excess cancers could not be expected to be detected against the background of natural rates.

#### 5.4 Recent Reports on Plutonium Effects in U.S. Workers at Los Alamos

A more recent paper on Los Alamos workers exposed to both plutonium and external radiation was published by [Wiggs et al. \(1994\)](#). The study concerns 15,727 workers, of whom 3196 had died by 1990 and were available for evaluation. The overall mortality in this group was low, with a standard mortality ratio (SMR) of 63% for all causes and 64% for all cancer. Lung cancer was a very low 45%. A total of 3775 workers were monitored for plutonium and 303 of these were classified as “exposed” with body burdens of greater than 74 Bq (equivalent to 16 mGy to the lung). Comparing mortality in exposed and unexposed groups gave a rate ratio ([Wiggs et al. 1994](#)) for all causes of 0.89 (95% CI = 0.69–1.14); for all cancers of 1.07 (95% CI = 0.67– 1.69); and for lung cancer of 1.78 (95% CI = 0.79–3.96). The latter result was not

**Follow up of plutonium workers in the United States has not indicated any health effects from exposure to low-levels of plutonium.**

significant and the trend with dose was not positive. Some other cancer sites (such as the mouth, rectum, and bladder) had higher nonsignificant rate ratios. There was no apparent excess of bone cancers (4 observed versus 3.9 expected) but this was one of the few sites with an SMR of 100% or more. One of the bone tumors is a well- studied osteosarcoma, occurring in 1 of the 26 Manhattan Project workers described by [Voelz and Lawrence \(1991\)](#). Some of the 303 workers exposed to plutonium also had

external low-LET exposure. To find the effect of plutonium alone, workers with more than 10 mSv external exposure were excluded. This left only 136 workers, and in these workers no rate ratios were found to be significant. The rate ratios for lung cancer dropped to 1.04 (95% CI = 0.20– 3.57). Taken together these results do not indicate an effect of plutonium even for lung cancer. However, follow up of these workers will continue.

In the larger number of Los Alamos workers exposed to external radiation, statistically significant results were found for three cancers: Hodgkins disease (not normally associated with radiation [BEIR V, [NAS/NRC 1990](#)]); malignancies of the brain (Note a marginally significant result for malignancies of the brain in rats was found by [Sanders et al. 1992](#)); and cancers of the oesophagus. A nonsignificant result for cancer of the kidney became significant when those exposed to plutonium were excluded from the analysis. However, a positive result was not found for the bladder. These results will also be reexamined after further follow up. To conclude, presently no clear-cut effect of plutonium is evident in the Los Alamos worker study after 29 years of follow up. [Table 5-2](#) summarizes the U.S. epidemiological studies.

**Table 5-2. Epidemiological Studies of U.S. Workers Exposed to Plutonium**

Study	Population	Number	Status or comment	Result
<a href="#">Wilkinson et al.</a> 1987	Workers, Rocky Flats	5413 males	External exposure 41 mGy Pu 65 Bq	No elevated rates for lung cancer or bone cancer
<a href="#">Voelz et al.</a> 1985; <a href="#">Voelz and Lawrence</a> 1991	Workers, Los Alamos	(1) 26 (2) 224	-- Fewer deaths than expected	No significant excess of lung cancer <sup>a</sup>
<a href="#">Tietjen</a> 1987	Workers, Los Alamos, Rocky Flats and Mound	---	---	Lung cancer lower than controls
<a href="#">Wiggs et al.</a> 1994	Workers, Los Alamos	15,727	Plutonium and external radiation 303 >74 Bq Pu	No excess cancers due to plutonium

<sup>a</sup> One osteosarcoma observed

Some Los Alamos workers are included in a recent review of causes of death among participants in the United States Transuranium and Uranium Registries (USTUR). The following report is abstracted from [Gold and Kathren](#) (1998).

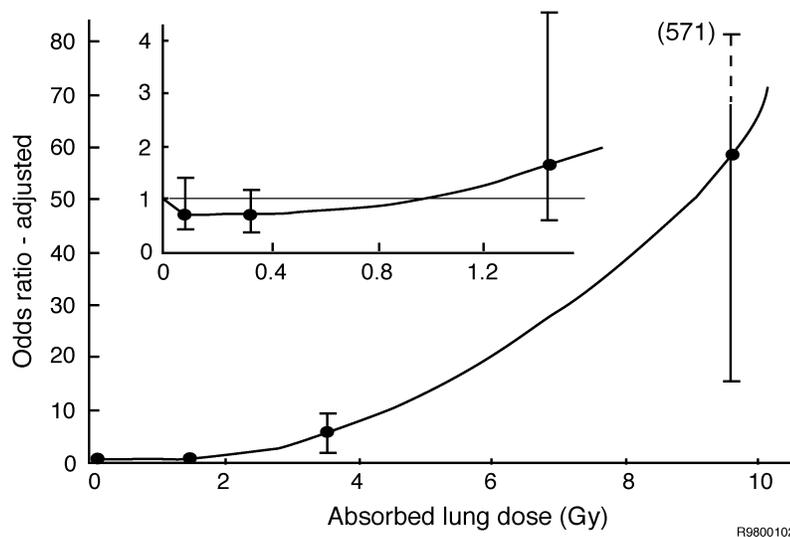
The USTUR is a unique postmortem research study of the biokinetics, dosimetry, and possible biological effects of actinide elements in persons with occupational exposure to these radioelements. Evaluation of the causes of death in the admittedly biased self-selected cohort of the first 260 deceased participants in the USTUR revealed, in general, no apparently elevated causes of death except for six cases of mesothelioma and six cases of astrocytoma glioblastoma multiforme. The mesothelioma cases had a documented occupational exposure to asbestos, and the six brain tumor deaths all occurred at a single work site (Rocky Flats) and were not radiation related but rather are likely attributable to a factor specific to the work site or surrounding area. Incidental findings in this cohort did not suggest any radiation related illness or cause of death.

### 5.5 Further Studies on Russian (Mayak) Workers Exposed to Plutonium

A number of additional studies of lung cancer in the Mayak workers, particularly those exposed to plutonium, have been published in recent years. The first is a case control study of 162 cases (148 male 14 female) of lung cancer in the workers at Mayak. These were matched with 338 controls (296 male 42 female) among workers without disease ([Tokarskaya et al.](#) 1995). The males had similar external exposures: 1.66 Gy in workers with cancer and 1.46 Gy in workers in the control group. However, the workers with cancer had higher plutonium absorbed doses to the lung of 0.94 Gy compared to 0.30 Gy in the control group (i.e., 19 Sv versus 6 Sv).

The external dose to females with lung cancer was 2.0 Gy compared with 1.02 Gy in the control group, and the plutonium dose was 9.1 Gy compared with 0.96 Gy (i.e., 182 Sv versus 19 Sv). Smoking histories were documented and the histology of the cancers identified. Attributable risks were established for different types of lung cancer and for smoking. For smoking the odds ratio for squamous cell carcinomas is 6.8, larger than any other association. Adenocarcinomas dominated in the groups exposed to higher levels of plutonium, whereas small cell carcinomas tended to dominate in atomic bomb survivors and miners exposed to radon ([Land et al. 1993](#)). It is not clear if the same cells in the lung are irradiated with plutonium deposited via different particle sizes as those irradiated by radon progeny. A relative risk of 3.1 (95% CI = 1.8–5.1) was found for 60 cases with plutonium body burdens of 5.6 to 141 kBq, which corresponds to a dose range of 1.5 Gy to 34 Gy to the lung. In addition, pneumosclerosis was seen in cases with  $^{239}\text{Pu}$  burdens of 18.5 kBq delivering about 5 Gy to the lung and more.

In a later case control study of exactly the same case material by the same authors ([Tokarskaya et al. 1997](#)) multifactorial analyses were made of the dose-response relationships. A linear response was found for smoking (versus frequency). No clear cut response could be found for gamma radiation alone. For incorporated plutonium linear quadratic or quadratic models could describe the response. As shown in Figure 5-1 the odds ratio did not increase until a dose of about 1 Gy is reached. The response is essentially the same for three histological types, adenocarcinoma, squamous cell carcinoma and small-cell cancer. In the analysis the authors determined a threshold for the onset of lung cancer of 3.7 kBq of incorporated plutonium or an absorbed dose of 0.8 Gy to the lung. The authors point out that their dose response is very similar to that found by [Sanders et al. \(1988c\)](#) for lung tumors in rats following  $\text{PuO}_2$  exposure.

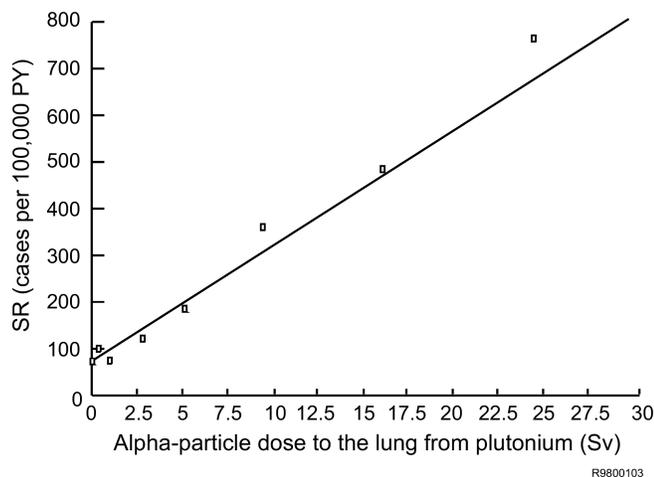


**Figure 5-1.** Risk (odds ratio-adjusted) of lung cancer, depending on absorbed lung dose, caused by  $^{239}\text{Pu}$  incorporation ([Tokarskaya et al. 1997](#)).

Another perspective on the response of Mayak workers to plutonium is obtained from reports on cohort studies. The first report of [Hohryakov and Romanov \(1994\)](#) on radiochemical workers has been discussed earlier. [Koshurnikova et al. \(1996\)](#) then reported on lung cancer

mortality in men at the radiochemical plants at Mayak and in both men and women at the plutonium production plant. The plutonium burdens were known in each case. The excess relative risk per Sv was 0.36 for males with a lung dose less than 7.5 Sv and 0.22 for males with a lung dose greater than 7.5 Sv. For the fewer females the results were  $-0.046$  and  $0.44$  for lung doses below and above 7.5 Sv, respectively. In a later paper ([Koshurnikova et al. 1997](#)), a linear response of lung cancer mortality with dose was found for the 105 lung tumors in males with known plutonium body burdens. The linear response for males yielded an annual risk of 28.4 cases per  $10^5$  PYSv or  $1.42 \times 10^{-2}$   $\text{Sv}^{-1}$  lifetime risk based on a 50-y period at risk following exposure. The corresponding result for the fewer females (15 lung tumors) with known plutonium body burdens was  $0.35 \times 10^{-2}$   $\text{Sv}^{-1}$  for the lifetime lung cancer risk. Smoking, however, was a confounder which affected males more than females.

In a still later report ([Koshurnikova et al. 1998](#)), the same cohort of males was reanalyzed and presented in more detail (the females were not included). The results for doses up to 30 Sv are shown in Figure 5-2. Results are also available for much higher doses but the response tends to fall off, presumably due to cell killing (see [Koshurnikova et al. 1998](#), Figure 2). Figure 5-2 shows an impressive linear response, unfortunately, uncertainties were not evaluated in detail and no error bars are provided on the points. Details of the dosimetry, which is based on serial urine analysis and models, and of the statistical methods employed are still not fully available and the effects of smoking have not yet been accounted for. Nevertheless, a definite response between lung cancer mortality and estimated equivalent dose to the lung from plutonium seems to have been obtained. The actual absolute risk obtained is  $24.2 \pm 1.8$  cases for  $10^5$  PYSv, which for a 50 year period at risk (the authors did not use lifetables) gives a lifetime risk of lung cancer of  $1.21 \times 10^{-2}$   $\text{Sv}^{-1}$  for males.



**Figure 5-2.** Lung cancer mortality in the study cohort as a function of alpha particle dose to the lung (dose range below 30 Sv). SR is the age standardized lung cancer mortality rate. Preliminary estimates of the parameters of the relationship between dose and lung cancer mortality by regression analysis with weighting of the mortality rates for each dose category by the number of person-years in the category ([Koshurnikova et al. 1998](#)).

It is not easy to reconcile the results of the cohort studies with those of the case control studies. The dosimetry, based on serial urine analysis, was the same in both cases although few details are available. However, the two populations studied were not exactly the same. In the case control studies (Tokarskaya et al. [1995](#), [1997](#)) 162 cases of lung cancer were apparently all the cases of lung cancer in the total Mayak worker population at risk. This presumably included those exposed to plutonium alpha radiation plus gamma radiation, gamma radiation alone and perhaps some with virtually no exposure. The cohort studies (Koshurnikova et al. [1996](#), [1997](#), [1998](#)) focused on a population with the largest plutonium exposures (105 males with lung cancer and 15 females with lung cancer, presumably part of the 160 cases in the case control study) and for whom the plutonium exposures were known. The plutonium production workers and the radiochemical workers with the greatest plutonium burdens were called “plutonium carriers” in the latest cohort study ([Koshurnikova et al. 1998](#)) and presumably represent the population most specifically exposed to plutonium and less to other sources including gamma rays.

Both studies find a substantial effect of plutonium in inducing lung cancer at high doses. The case control study implicates adenocarcinomas especially among the three histological types described. At low doses the case control study finds essentially no lung cancers and derives a threshold of 3.7 kBq plutonium or 0.8 Gy to the lung. At this same dose (0.8 Gy = 16 Sv, with an RBE of 20) the cohort study shows a clear non-zero risk of mortality from lung cancer of about 450 cases per 100,000 against a background of only about 75 cases per 100,000 ([Figure 5-2](#)). Perhaps because of the choice of study population the cohort studies appear to be able to provide information at lower doses than the case control studies. Error bars are provided on the graphs of the case control study but it is not certain what they include, possibly statistical uncertainties only. The main features of the results of the Mayak worker studies are shown in Table 5-3.

**Table 5-3. Epidemiological Studies of Mayak Workers**

Reference	Worker type	Study type	Number	Exposure	Result
<a href="#">Hohryakov &amp; Romanov</a> (1994)	Radiochemical	Cohort	2346 (1832 male 514 female)	>4 Sv, about 1/4 due to Pu	Lifetime lung cancer risk $1.4 \times 10^{-2} \text{ Sv}^{-1}$
<a href="#">Tokarskaya et al.</a> (1995)	Exposed group with lung cancer	Case control	162 (148 male 14 female)	60 cases with Pu >5.6 kBq	Relative risk of lung cancer = 3.1
<a href="#">Tokarskaya et al.</a> (1997)	Exposed group with lung cancer	Case control	162 (148 male 14 female)	60 cases with Pu >5.6 kBq	Threshold 0.8 Gy
<a href="#">Koshurnikova et al.</a> (1997)	Plutonium workers	Cohort	1479 males  666 females	6.6 Sv (Pu)  12.6 Sv (Pu)	Lifetime lung cancer risk $1.4 \times 10^{-2} \text{ Sv}^{-1}$ $0.35 \times 10^{-2} \text{ Sv}^{-1}$
<a href="#">Koshurnikova et al.</a> (1998)	Plutonium workers	Cohort	1479 males	6.6 Sv (Pu)	Lifetime lung cancer risk $1.2 \times 10^{-2} \text{ Sv}^{-1}$

For Rocky Flats exposures to the public, which are all at very low dose, the risk is either zero (because the doses are below a threshold) or has the value given by the cohort studies, i.e. about  $1.0 \times 10^{-2} \text{ Sv}^{-1}$  for both sexes. We shall assume the latter.

## 5.6 Conclusion for Plutonium and Lung Cancer

U.S. and U.K. studies of plutonium workers exposed to relatively low levels of plutonium have not shown clear evidence of the effects of plutonium. Russian studies involve workers with much higher doses. These include radiochemical workers in whom the exposure was mainly to external gamma radiation, only 1/4 to 1/3 of their exposure being due to plutonium alpha particles. Nevertheless, using an RBE of 16 and a combined dose estimate a lifetime risk of lung cancer due to plutonium alpha particles was found to be about  $1.4 \times 10^{-2} \text{ Sv}^{-1}$  (Hohryakov and Romanov 1994). Workers involved in plutonium production appear to have much more of their exposure due to plutonium alpha particles than to gamma rays, about 6 times greater. Studies of a worker cohort of plutonium “carriers” yield a risk (RBE = 20) of  $1.4 \times 10^{-2} \text{ Sv}^{-1}$  for 105 males with lung cancer and  $0.35 \times 10^{-2} \text{ Sv}^{-1}$  for 15 females with lung cancer (Koshurnikova et al. 1997). A later more detailed re-analysis of the male workers in this cohort yielded a lifetime risk of about  $1.2 \times 10^{-2} \text{ Sv}^{-1}$  (Koshurnikova et al. 1998). These values compare with the ICRP value for lung cancer in adult workers of  $0.68 \times 10^{-2} \text{ Sv}^{-1}$  (ICRP 1991).

It is difficult to place an estimate of uncertainty on these results for plutonium induced lung cancer in the Mayak workers. The association between lung cancers and dose is very strong at high doses. At low doses it appears linear in the cohort studies but more like a threshold (at 0.8 Gy) in the case control studies. The choice of study population favors the cohort study. The uncertainties here are at least as great as the uncertainties in the low-LET risk derived from the atomic bomb survivors. All the same factors, except perhaps the DDREF, apply but are less well known. For example, the dosimetry is based on serial urine samples and a model for the dose to the lung. There is little information on the variability of the samples for each individual and between individuals although recently Anspaugh expressed the uncertainty as having a GSD of 2.8 (Anspaugh 1997). There are uncertainties also in the epidemiological methodology and in the crude estimate of lifetime risk from the observed period of risk. Smoking is an important confounder that has not yet been evaluated. The difference between the male risk and female risk in Koshurnikova et al. (1997) may be due, at least in part, to smoking. Inevitably the risk due to plutonium in males will be lower when smoking is accounted for. Although the result for females is regarded as less certain because of the relatively few female lung cancer cases (15) it may not be unreasonable to average male and female, i.e., the lifetime risk for both sexes is about  $1.0 \times 10^{-2} \text{ Sv}^{-1}$ .

This result, important as it is because of its direct derivation from actual plutonium exposures, must be considered uncertain by at least a factor of 4 in either direction, i.e. the 2.5 and 97.5 percentiles of the distribution range from  $0.25 \times 10^{-2} \text{ Sv}^{-1}$  to  $4 \times 10^{-2} \text{ Sv}^{-1}$ , respectively. As time goes on and further details become available, it may be possible to make a more definite estimate of uncertainty. The risk result is given per sievert but for our purposes here it is more useful per gray. Since an RBE of 20 was used, the central value of the lifetime lung cancer risk is  $20 \times 10^{-2} \text{ Gy}^{-1}$  with a range from  $(5 \text{ to } 80) \times 10^{-2} \text{ Gy}^{-1}$ .

**An excess risk of lung cancer has been observed in the Mayak workers, however, no excess risk of liver or bone cancers has been observed.**

### 5.7 Organs Other Than the Lung

The epidemiological studies described above lead directly to risk estimates for the lung; however, none of the studies found an excess of bone or liver tumors. Bone doses to some of the workers should be about twice as great as the lung dose and liver doses about half as great as the lung dose. The nominal absolute risks of these radiation-induced cancers per unit dose are, however, about 1/17 and 1/6, respectively of the lung tumor risks. Consequently, fewer tumors would be expected to be induced. For bone the number of tumors would be about 1/8 that of lung and for liver the number of tumors would be about 1/12 that of lung. Detectability is determined also by the natural risk of these tumors in the population or the relative risk of a radiation-induced tumor. For bone the relative risk per sievert is about 1½ times that for lung and for liver it is only about ½ that of lung ([Pierce et al. 1996a](#)). It seems possible that although the number of bone tumors to be expected is much smaller, given the number of lung tumors found and the relative risk for bone tumors an excess for bone cancer might have been detected also. However, no excess of bone cancer was reported. In the case of liver cancer it is less likely that an excess would be detectable.

## 6. LOW-LET RISK ESTIMATES FROM THE ATOMIC BOMB SURVIVORS COMBINED WITH ALPHA PARTICLE RBE VALUES

This chapter describes the second of the four approaches used in this report to estimate the cancer risk from plutonium exposures. This approach is based on the low-LET radiation risk coefficients determined from the atomic bomb survivors modified by an RBE, to account for the relative biological effectiveness of the high-LET radiation emitted by plutonium.

[Section 6.1](#) provides an overview of the Lifespan Study (LSS). [Section 6.2](#) examines the present status of the LSS to derive lifetime risk coefficients for low-LET radiation for the Japanese atomic bomb survivors for lung, liver, bone, bone marrow, and whole body. These risk coefficients provide the starting point on which the subsequent analysis of uncertainties is based. [Section 6.3](#) identifies and quantifies the factors that contribute to the uncertainty in the low-LET risk coefficients derived from the LSS. These uncertainties encompass epidemiology, dosimetry, lifetime risk projection, transfer of risk to other populations, and dose and dose rate effects. [Section 6.4](#) considers the relevant information on the likely RBE values for plutonium alpha particles for each organ of interest, chooses median values, and assesses the uncertainties. [Section 6.5](#) combines the low-LET risk coefficient distributions determined in [Section 6.3](#) and the distribution of RBE values determined in [Section 6.4](#) to generate an estimate of the lifetime risk coefficients for lung, liver, bone, and bone marrow for plutonium inhalation exposures at Rocky Flats. The uncertainties in these lifetime risk coefficients are carefully evaluated and a sensitivity analysis is provided. Readers interested primarily in the distribution of lifetime risk coefficients that are derived using this approach may prefer to turn directly to [Section 6.5](#).

### 6.1 Overview of the Lifespan Study

The risk coefficients most widely used in radiation protection and other applications are largely based on the LSS of the Japanese survivors of the atomic bombs dropped in 1945. These risk estimates are for mainly low-LET radiation. In atomic explosions, both low-LET gamma rays and high-LET neutrons are released and delivered at a high dose rate. For the survivors at Hiroshima and Nagasaki, the Dosimetry System 1986 (DS86) ([Roesch](#) 1987) is used to estimate the doses received. At representative distances from the explosion, the system describes the organ-absorbed dose as 98–99% due to gamma rays and only 1–2% due to neutrons (see [Section 6.3.2.2](#)).

The LSS includes approximately 93,000 persons of all ages who survived the atomic bombings at Hiroshima and Nagasaki. Almost 70% of the survivors were in Hiroshima and about 30% were in Nagasaki. The study has focused mainly on deaths due to cancer, which have been evaluated at approximately 5-year intervals beginning in 1950. The 1996 update of the mortality study ([Pierce et al.](#) 1996a) included data from 1950–1990. Data on the incidence of cancer in this LSS population have also become available from tumor registries in Hiroshima and Nagasaki for the period 1958–1987 for solid tumors ([Thompson et al.](#) 1994) and 1950–1987 for hematopoietic tumors ([Preston et al.](#) 1994). Comparisons between incidence and mortality were made using comparable periods of follow-up ([Ron et al.](#) 1994a). At the end of 1987, approximately 60% of the survivors were still alive and their average age was about 60 years.

**The Japanese survivors of the atomic bombings at Hiroshima and Nagasaki were exposed to gamma rays and neutrons delivered to the whole body at a high dose rate.**

Table 6-1 summarizes the observed cancer incidence (up to 1987) and death (up to 1985) in the control group, which received doses <0.01 Gy (<1 rad), and in the exposed group, with doses ranging from 0.01–4 Gy (1–400 rad). Survivors with dose estimates in excess of 4 Gy were excluded from the analysis because of questions about the accuracy of those dose estimates and the problem of cell killing at these doses. The incidence data are from [Thompson et al.](#) (1994) and [Preston et al.](#) (1994); the tabulation of cancer deaths is from [Shimizu et al.](#) (1988) and [Sinclair](#) (1993b) and covers a different time interval. Unfortunately, insufficient information is provided in the source documentation to compile the data for incidence and mortality over the same time period. The sizes of the control and exposed groups also differ somewhat. The number of cancer cases attributable to the exposure was based upon a calculation of expected numbers of cancers in various dose categories, using an excess relative risk model that included the effects of age and gender. The sum of the numbers of cancers expected in each dose category was then subtracted from the observed number of cancers to obtain the number attributable to exposure shown in the last column of Table 6-1.

**Table 6-1. Cancer Incidence (1958–1987) and Death (1950–1985)  
in the LSS Cohort of Atomic Bomb Survivors**

Category	Control group (<0.01 Gy)	Exposed group (0.01–4 Gy)	Total	Cancers attributable to exposure
Cancer incidence (1958–1987)				
Persons	39,213	40,759	79,972	—
All cancer	4,376	4,468	8,844	578
Leukemia	90	141	231	75
Solid tumors	4,286	4,327	8,613	503
Cancer deaths (1950–1985)				
Persons	34,272	41,719	75,991	—
All cancer	2,502	3,435	5,936	339
Leukemia	58	144	202	80
Solid tumors	2,443	3,291	5,734	259

The incidence data are presented in more detail in [Table 6-2](#), which shows the percentage of total solid tumors in the study cohort, the excess relative risk of cancer incidence at 1 sievert ( $ERR_{1Sv}$ ), and the excess absolute risk of cancer incidence per 10,000 PYSv for many cancer sites ([Thompson et al.](#) 1994). The detailed site listings include about 97% of the total solid tumors. An additional 254 cancers were located at other or ill-defined sites. Grouping by organ system shows cancers of the digestive system are dominant for the Japanese population. Within the digestive system, stomach, colon, and liver cancer risks were significant. Cancers of the respiratory system accounted for more than 10% of the total solid tumors. As expected, uncertainties in the risk estimates for individual sites exceed those for organ systems or for all tumors combined. This increased variance affects the reliability of estimates for the specific organs of interest at Rocky Flats. For reference, [Table 6-2](#) also includes the  $ERR_{1Sv}$  for leukemia ([Preston et al.](#) 1994).

**Table 6-2. Excess Relative Risk and Excess Absolute Risk of Cancer Incidence (1958–1987) by Cancer Site or Organ System in the Atomic Bomb Survivors (taken from Table X, [Thompson et al. 1994](#) and Table II, [Ron et al. 1994a](#))**

Cancer site or organ system	Percentage of all tumors	Excess relative risk at 1 Sv <sup>a</sup> (ERR <sub>1Sv</sub> )	Excess absolute risk per 10,000 PYSv <sup>a</sup>
Total solid cancers	95.5 <sup>b</sup>	0.63 (0.52–0.74)	29.7 (24.7–34.8)
Oral cavity and pharynx	1.5	0.29 (–0.09–0.93)	0.23 (–0.08–0.65)
Digestive system	53.2	0.38 (0.25–0.52)	10.4 (7.0–14.0)
Esophagus	2.0	0.28 (–0.21–1.0)	0.30 (–0.23–1.0)
Stomach	29.5	0.32 (0.16–0.50)	4.8 (2.5–7.4)
Colon	5.0	0.72 (0.29–1.3)	1.8 (0.74–3.0)
Rectum	3.9	0.21 (–0.17–0.75)	0.43 (–0.35–1.5)
Liver	6.5	0.49 (0.16–0.92)	1.6 (0.54–2.9)
Gallbladder	3.3	0.12 (–0.27–0.72)	0.18 (–0.41–1.1)
Pancreas	2.7	0.18 (–0.25–0.82)	0.24 (–0.36–1.1)
Respiratory system	11.4	0.80 (0.50–1.2)	4.4 (2.9–6.1)
Trachea, bronchus, and lung	9.7	0.95 (0.60–1.4)	4.4 (2.9–6.0)
Nonmelanoma skin	1.9	1.0 (0.41–1.9)	0.84 (0.40–1.4)
Female breast	5.9	1.6 (1.1–2.2)	6.7 (4.9–8.7)
Uterus	8.0	–0.15 (–0.29–0.10)	–1.1 (–2.1–0.68)
Ovary	1.5	0.99 (0.12–2.3)	1.1 (0.15–2.3)
Prostate	1.6	0.29 (–0.21–1.2)	0.61 (–0.46–2.2)
Urinary organs and kidney	3.6	1.2 (0.62–2.1)	2.1 (1.1–3.2)
Urinary bladder	2.3	1.0 (0.27–2.1)	1.2 (0.34–2.1)
Kidney	0.8	0.71 (–0.11–2.2)	0.29 (–0.50–0.79)
Nervous system	1.4	0.26 (–0.23–1.3)	0.19 (–0.17–0.81)
Thyroid	2.5	1.2 (0.48–2.1)	1.6 (0.78–2.5)
Leukemia (1950–1987) <sup>c</sup>	1.9	4.4 (3.2–5.6) <sup>d</sup>	2.8 (2.0–3.5) <sup>d</sup>

<sup>a</sup> The 95% confidence interval is shown in parentheses.

<sup>b</sup> The remaining 4.5% are hemato-lymphopoietic with leukemia accounting for 1.9%

<sup>c</sup> [UNSCEAR](#) (1994) using data published in [Preston et al.](#) (1994)

<sup>d</sup> The 90% confidence interval is shown in parentheses.

[Table 6-3](#) gives a similar listing of the ERR of cancer mortality for the same time period for many of the same solid tumor sites ([Ron et al.](#) 1994a). [Table 6-3](#) does not include cancer sites for which there were no excess deaths. The results in [Tables 6-2](#) and [6-3](#) also include the excess absolute risk (EAR) over the observation period (per 10<sup>4</sup> PYSv). Note that the following

calculations are based on the more complete mortality data for the period 1950–1987 ([Ron et al. 1994a](#)).

**Table 6-3. Excess Relative Risk and Excess Absolute Risk of Cancer Mortality (1958–1987) by Cancer Site or Organ System in the Atomic Bomb Survivors (taken from [Ron et al. 1994a](#), Table VII)**

Cancer site or organ system	Excess relative risk at 1 Sv ( $ERR_{1Sv}$ ) <sup>a</sup>	Excess absolute risk per 10,000 PYSv <sup>a</sup>
Total solid cancers	0.46 (0.34–0.58)	12.4 (9.3–15.7)
Oral cavity and pharynx	-0.16 (<-0.16–0.32)	-0.06 (<0.06–0.11)
Digestive system	0.32 (0.18–0.46)	5.6 (3.2–8.1)
Esophagus	0.49 (-0.1–1.37)	0.42 (-0.1–1.1)
Stomach	0.21 (0.046–0.40)	2.0 (0.45–3.8)
Colon	0.57 (0.09–1.3)	0.64 (0.11–1.3)
Liver	0.50 (0.19–0.88)	1.5 <sup>b</sup> (0.60–2.5)
Respiratory system	0.63 (0.34–0.99)	2.5 (1.4–3.7)
Trachea, bronchus and lung	0.67 (0.35–1.1)	2.3 (1.3–3.5)
Nonmelanoma skin	0.42 (-0.15–2.2)	0.049 (-0.019–0.20)
Female breast	1.5 (0.66–2.6)	1.6 (0.78–2.5)
Uterus	0.044 (-0.26–0.51)	0.12 (-0.73–1.3)
Ovary	1.4 (0.28–3.2)	0.90 (0.21–1.8)
Prostate	0.28 (<-0.26–1.6)	0.21 (<0.21–1.1)
Urinary organs and kidney	1.3 (0.44–2.7)	0.79 (0.29–1.4)
Urinary bladder	1.5 (0.29–3.4)	0.56 (0.13–1.1)
Nervous system	0.61 (<-0.23–2.5)	0.17 (<0.070–0.55)
Thyroid	0.016 (-0.23–1.5)	0.0032 (-0.048–0.26)
Leukemia (1950–1985)	5.21 (3.83–7.12) <sup>b</sup>	

<sup>a</sup> The 95% confidence limits are shown in parentheses.  
<sup>b</sup> Taken from [Shimizu et al. \(1988\)](#)  $ERR_{1 Gy}$  (organ-absorbed dose) with 90% confidence limits in parentheses.

## 6.2 Low-LET Lifetime Risk Coefficients Determined from the LSS Data

The lifetime mortality risk coefficient for all cancers ( $R_{JWB}$ ) following a whole-body acute exposure of 1 Sv that is determined from the atomic bomb survivors is  $12 \times 10^{-2}$  (Table 32, [UNSCEAR 1994](#)). This value was calculated by [UNSCEAR \(1994\)](#) using the LSS cancer mortality data for 1950–1987 presented by [Ron et al. \(1994a\)](#) and the LSS pooled leukemia data presented by [Preston et al. \(1994\)](#). To project to the lifetime risk, the age distribution of the population was assumed to be that of Japan in 1985. The lifetime mortality risk for all cancers except leukemia was calculated to be  $10.9 \times 10^{-2}$  using a constant relative risk model. The lifetime mortality risk of leukemia following a whole-body acute exposure of 1 Sv was calculated to be  $1.1 \times 10^{-2}$  using a linear-quadratic dose-response model. This means that, on average, for every sievert of radiation to which the survivors were exposed, any individual in that population

is estimated to have a 12% ( $10.9 + 1.1$ ) probability of developing and dying from cancer during his or her lifetime as a result of the radiation exposure. The lifetime fatal risk coefficients for the specific cancer sites of interest for plutonium exposure are given by,  $R_{Ji}$ , where J indicates a Japanese population, and i represents the cancer site of interest: L = lung, LV = liver, B = bone, LK = leukemia (bone marrow), and WB = (whole body) for total cancer.

In most cases the risk estimates derived from the atomic bomb survivors are presented on a percent per sievert basis rather than a percent per gray basis. This is because an RBE value of 10 is generally assumed for the neutron dose component. As noted earlier, the neutrons contribute only a small fraction (~1–2%) of the total absorbed dose. [Section 6.3.2](#) considers the uncertainty in the risk estimates because of uncertainty in the neutron dose. This chapter presents the risk estimates for the organs of interest in [Table 6-4](#) derived from the LSS as described below. Because the risk estimates are primarily for exposure to low-LET gamma radiation, it is assumed that the reported risk per sievert is equal to the risk per gray.

**Table 6-4. Lifetime Risk Coefficients for Fatal Cancer for Exposure of the LSS Cohort to Low-LET Radiation at High Dose Rates**

Cancer site	Lifetime risk of fatal cancer ( $10^{-2} \text{ Gy}^{-1}$ )
Lung ( $R_{JL}$ )	2.0
Liver ( $R_{JLV}$ )	1.0
Bone ( $R_{JB}$ )	0.03
Bone marrow ( $R_{JLK}$ )	1.1
Whole body ( $R_{JWB}$ )	12.0

The site-specific lifetime risk for liver and lung cancer mortality have been determined as follows. Starting with [UNSCEAR](#) (1994), a lifetime risk of 2.5% per sievert for lung cancer and 1.2% per sievert for liver cancer was calculated using the LSS cancer mortality data for 1950–1987 and the same projection method as for all tumors. The ERR values at 1 Sv on which these calculations were based were 0.65 (95% confidence interval [CI] = 0.34–1.0) for lung and 0.46 (95% CI = 0.18–0.81) for liver (1950–1987 data, see [Ron et al.](#) 1994a). Next, in the most recent analysis using the LSS mortality data for 1950–1990, these ERR values decreased slightly, but not significantly, to 0.53 (95% CI = 0.28–0.84) and 0.37 (95% CI = 0.13–0.65), respectively ([Pierce et al.](#) 1996a). Assuming that the latest lifetime risk coefficient figures would be proportional to the ERR values these coefficients become 2% per sievert for lung and 1% per sievert for liver.

It is not necessary to revise the risk coefficient for leukemia ( $R_{JLK}$ ) as it remains essentially unchanged.

No statistically significant ERR of bone cancer was detected in the analysis of the LSS mortality data for 1950–1987. In the analysis by [Pierce et al.](#) (1996a) for the follow-up period 1950–1990, positive point estimates are given for both ERR and EAR of bone cancer. However, there is no estimate of the corresponding lifetime risk coefficient. A provisional value for use in our calculations can be estimated by multiplying the EAR ( $0.08 \times 10^{-4} \text{ PYSv}$ ) by the period of expression of this risk. The period of expression for bone tumors should be more than for leukemia, but the period of expression is well known to be less than for other solid tumors ([NIH](#) 1985). If 40 years is taken to be a reasonable value for this period of expression, the approximate

lifetime risk for fatal bone cancer is  $40 \text{ years} \times 0.08 \times 10^{-4} \text{ PYSv}$  or  $0.032 \times 10^{-2} \text{ Sv}^{-1}$ . Dale Preston made a recent calculation of lifetime risk for bone when the age at exposure is 30 years ([Preston 1997](#)). The calculation yielded a value of about  $0.022 \times 10^{-2} \text{ Sv}^{-1}$ . In view of the large uncertainties involved, we will use  $0.03 \times 10^{-2} \text{ Sv}^{-1}$  and this value is entered in [Table 6-4](#).

Given all of the above, lifetime risk coefficient values of 2.0% per sievert for lung ( $R_{\text{L}}$ ), 1.0% per sievert for liver ( $R_{\text{LV}}$ ), and 0.03% per sievert for bone ( $R_{\text{B}}$ ) are considered good selections for our analysis. These values are based on consideration of data from RERF reports for 1990 ([Shimizu et al. 1990](#)), 1994 ([Ron et al. 1994a](#)), and 1996 ([Pierce et al. 1996a](#)) as described above, except for leukemia and whole body, which are taken directly from [UNSCEAR \(1994\)](#) and have not changed in later evaluations.

### 6.3 Uncertainties in the Low-LET Lifetime Risk Coefficients for the U.S. Population

Selecting the most appropriate risk factors with uncertainty estimates for exposure of a U.S. population to low-LET radiation requires critical consideration of a number of factors. Every effort has been made to identify all the factors that contribute to bias and uncertainty in the risk estimates, but inevitably we cannot account for some uncertainties. The key sources of uncertainties inherent in the statistical analysis of lifetime risk derived from the LSS data are

- Epidemiological uncertainties, [Section 6.3.1](#)
- Dosimetric uncertainties, [Section 6.3.2](#)
- Lifetime risk projection uncertainties, [Section 6.3.3](#).

Other factors giving rise to uncertainties relate to differences in the exposure circumstances and in the characteristics of the exposed populations. The key differences are the

- Uncertainties in transferring risk factors based upon exposure of a Japanese population to a U.S. population, [Section 6.3.4](#)
- Differences in the dose and dose rate for the two exposure situations, [Section 6.3.5](#).

This section considers each factor listed above. The individual organ risks for lung, liver, bone, and leukemia are assessed, as well as the whole-body risk. For each uncertain factor identified, a subjective probability distribution function is developed. In those cases where data are limiting, upper and lower bounds to the uncertainties are defined. Each distribution is defined as a normalized distribution that is applied as a multiplicative factor to the risk estimate from the LSS (as given in [Table 6-4](#)). Each of the parameters is sampled randomly using a Monte Carlo technique to generate a revised distribution for the risk estimate. Combining all the uncertain parameters provides an estimate of the lifetime risk for low-LET exposures. The lifetime risk coefficient obtained from this calculation, however, is not directly applicable to individuals exposed to plutonium because plutonium emits alpha particles. [Section 6.4](#) discusses the RBE of high-LET plutonium alpha particles to low-LET radiations (x and gamma rays). [Section 6.5](#) combines the uncertainties in the low-LET lifetime risk coefficients with the uncertainties in the RBE values to generate estimates of the lifetime risk coefficients for plutonium inhalation exposures.

#### 6.3.1 Epidemiological Uncertainties

A number of factors contribute to epidemiological uncertainties. These include statistical uncertainties, statistical bias (i.e., possible misclassification and under- or overreporting of

cancer incidence or death), and selection bias (i.e., the question of whether the study population represents the population as a whole). Each factor is examined below and the uncertainties for each component are combined to derive the overall uncertainty associated with epidemiological factors.

**6.3.1.1 Statistical Uncertainties.** Statistical uncertainties are associated with quantifying the relatively small number of excess cancers attributable to ionizing radiation from the background of cancers resulting from all causes. As shown in [Table 6-1](#), the number of solid tumor cancer deaths attributed to exposure was 259 out of a total of 5734. In the most recent analysis of the mortality data, which includes an additional 5 years of follow up (1986–1990), this number has increased by 75 to 334 out of a total of 7578 ([Pierce et al. 1996a](#)). Although comparison of these data is not straightforward because the definition of the control group has changed from subjects exposed to doses <0.01 Gy to subjects exposed to doses <0.005 Gy, the attributable risk has remained essentially the same (4.5% versus 4.4%). This indicates that a constant relative risk has been maintained over this time period even though the sample size has been increased somewhat.

For our analysis, it is assumed that the lifetime risk coefficients derived from the LSS data have the same relative statistical uncertainties as the corresponding ERR and EAR values over the period of observation. Furthermore, we consider uncertainties only in the risk estimate for total cancers (whole body) or individual organs without regard to parameters such as age, gender, city etc. This is because we are interested, for this purpose only, in the uncertainties in risk for a population of all ages. The fractional uncertainties in both the  $ERR_{1Sv}$  and the EAR per 10,000 PYSv values are very similar; therefore, we consider only the  $ERR_{1Sv}$ . The  $ERR_{1Sv}$  of cancer mortality for specific sites is summarized in [Table 6-5](#) based on the LSS data for the two most recent follow-up time periods. The  $ERR_{1Sv}$  of cancer incidence is also included for comparison. A measure of the spread in the ERR estimates is given by the coefficient of variation (CV), which is calculated by dividing the standard deviation by the mean and expressing the result as a percentage (see [Glossary](#)). The  $ERR_{1Sv}$  for whole body was not reported in [Thompson et al. \(1994\)](#) for the 1958–1987 follow up; the reported value includes solid tumors, but it does not include leukemia. The more recent analysis of the LSS data reports the  $ERR_{1Sv}$  for all malignant neoplasms (whole body) with a 10% coefficient of variation. For our analysis a 15% CV in the whole body risk estimates is used to account for the statistical uncertainties.

**From 1950 through 1990 there have been 7578 deaths from solid cancers in the LSS. Of these, 334 are estimated to have resulted from the radiation exposure at the time of the bombings.**

The statistical uncertainties are larger for individual specific cancer sites than for the whole body because the number of cases is much smaller. Relatively large statistical uncertainties are associated with the liver (CV ~40%) and lung (CV ~30%) ([Table 6-5](#)).

No statistically significant association had been observed for bone cancer mortality in the LSS data up to 1985. Up to that time a total of 27 deaths from bone cancer had been recorded. However, estimates of the  $ERR_{1Gy}$  and EAR per 10,000 PYGy, with upper 95 percentile values only, were made ([Table 2B](#), [Shimizu et al. 1988](#)) based on the estimated dose to the whole body accounting for shielding by buildings (shielded kerma). The shielded kerma is somewhat different than the dose estimated to specific organs (organ-absorbed dose) that is used in our analysis when available because it does not account for absorption in the body. It is

approximately equivalent to the skin dose. The analysis of the data indicated a slight positive association, but as previously noted, this was not statistically significant. The coefficient of variation for the  $ERR_{1Gy}$  and EAR per 10,000 PYGy estimates is extremely large, reflecting the very large uncertainty in these estimates.

**Table 6-5. Site-specific Excess Relative Risk of Cancer (all Japan, organ-absorbed dose)**

Cancer site	$ERR_{1Sv}^a$	$ERR_{1Sv}^a$	$ERR_{1Sv}^b$
	1958–1987 incidence	1958–1987 mortality	1950–1990 mortality
Lung	0.95 (0.60–1.4) <sup>c</sup> CV 20% <sup>d</sup>	0.67 (0.35–1.1) CV 29%	0.53 (0.28–0.84) CV 27%
Liver (primary or not otherwise specified)	0.49 (0.16–0.92) CV 40%	0.50 (0.19–0.88) CV 35%	0.37 (0.13–0.65) CV 36%
Bone	Not reported	Not reported	0.86 (NA-3.70) <sup>e</sup> CV 170%
Total solid tumors	0.63 (0.52–0.74) CV 9%	0.46 (0.34–0.58) CV 13%	0.40 (0.31–0.51) CV 13%
Leukemia (bone marrow)	4.4 (3.2–5.5) <sup>f, g</sup> CV 13%	5.2 (3.8–7.1) <sup>h, g</sup> CV 16%	4.62 (3.28–6.40) CV 17%
Whole body	Not reported		0.53 (0.43, 0.64) CV 10%

<sup>a</sup> Taken from [Ron et al.](#) (1994a), Table VII.  
<sup>b</sup> Taken from [Pierce et al.](#) (1996a), Table AII.  
<sup>c</sup> Numbers in parentheses indicate the 95% confidence interval.  
<sup>d</sup> CV = coefficient of variation.  
<sup>e</sup> NA: Value is less than the minimum imposed by non-negativity constraints on the risk.  
<sup>f</sup> 1950–1987.  
<sup>g</sup> Taken from [UNSCEAR](#) (1994), Table 6.  
<sup>h</sup> 1950–1985.

The more recent analysis of cancer mortality in the atomic bomb survivors contains an extra 5 years of follow up ([Pierce et al.](#) 1996a) and reports positive point estimates of bone cancer risk but with broad uncertainty bounds. The coefficient of variation for the  $ERR_{1Sv}$  is approximately 170% based on the upper 95% value reported for the distribution. Thus, there is still large uncertainty in the reported risk estimate. Based on these results, for our analysis a large coefficient of variation (~150%) is assigned to bone for statistical uncertainties

In the analysis of the atomic bomb survivors by [Pierce et al.](#) (1996a), for the follow-up period 1950–1990, the  $ERR_{1Sv}$  for leukemia was calculated as 4.62 with a 20% coefficient of variation. An earlier analysis by [Shimizu et al.](#) (1990), for the follow-up period 1950–1985, calculated the  $ERR_{1Gy}$  of leukemia as 5.21 with a similar coefficient of variation (20%). In [Table 6-2](#) the  $ERR_{1Sv}$  for leukemia incidence is determined as 4.4 for the time period 1950–1987 ([Preston et al.](#) 1994). In the study of the incidence data in [Preston et al.](#) (1994), the different leukemia types were analyzed separately. There was strong evidence for radiation-induced risks for acute lymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous

leukemia. The estimated average excess relative risks at 1 Sv were 9.1, 3.3, and 6.2, respectively. There was no evidence of an excess risk for adult T-cell leukemia. Even though there were few cases of chronic lymphocytic leukemia in the LSS population, studies (Tomonaga et al. 1991) indicate that chronic lymphocytic leukemia is not radiation induced. For our analysis, a 20% coefficient of variation is assumed for the statistical uncertainties for leukemia taken as a whole.

The parameter  $f(S_i)$ , is used to account for the statistical uncertainties in the relative risk coefficient;  $i$  represents the cancer site of interest: L = lung, LV = liver, B = bone, LK = leukemia, and WB = (whole body) for total cancer. A normal distribution with a mean of 1 is used to describe the statistical uncertainties for the whole body and for leukemia, with a standard deviation of 0.15 and 0.20, respectively. For the remaining three sites that have larger statistical uncertainties (lung CV~30%, liver CV~40%, bone CV~150%), a lognormal distribution is used. This procedure avoids the potential selection of negative numbers that could occur if a normal distribution with a large coefficient of variation is assumed. The geometric mean (GM) of the distribution is set at 1 so that there is an equal chance of sampling values greater than 1 as values smaller than 1 and, thus, avoiding introducing bias in the uncertainty analysis. The geometric standard deviation (GSD) is defined (see [Glossary](#)) so that the lognormal distribution has approximately the same standard deviation as that observed in the data. For the lung and liver, the arithmetic mean of the assigned lognormal distribution is very close to 1. For the bone, which has an extremely large statistical uncertainty, a large GSD is assigned, but it results in a smaller standard deviation than that observed in the data (1.5 versus 1.7). This was considered a compromise; assigning a larger GSD would increase the arithmetic mean significantly beyond the current value of 1.4. Table 6-6 summarizes the distributions assumed for statistical uncertainties for each cancer site.

**Table 6-6. Summary of Statistical Uncertainties,  $f(S_i)$**

Cancer site	Distribution type	Distribution parameters <sup>a</sup>
Lung	Lognormal	GM = 1.0, GSD = 1.34
Liver	Lognormal	GM = 1.0, GSD = 1.44
Bone	Lognormal	GM = 1.0, GSD = 2.34
Bone marrow (leukemia)	Normal	m = 1.0, s = 0.20
Whole body	Normal	m = 1.0, s = 0.15

<sup>a</sup> GM = geometric mean, GSD = geometric standard deviation, m = mean, s = standard deviation.

**6.3.1.2 Statistical Bias.** Epidemiological data are often associated with statistical biases as a result of under- or overreporting the number of cancer cases and misclassifying cancer.

The mortality data for the LSS cohort are based on death certificates; however, the cause of death identified on death certificates is not always accurate. This deficiency has long been recognized, especially in people with age of death over about 60 years. As a group, cancer deaths are underreported by approximately 25%, however, this varies depending on the specific cancer type. For example, respiratory cancers are underreported by approximately 30% and hematopoietic cancers by about 15%. Liver cancer tends to be overstated on death certificates. The liver is often the target of metastases from cancers of other organs, with the result that some of these metastatic cancers are erroneously reported as primary cancers of the liver.

Although under- or overreporting affects the absolute measure of risk, the relative risk is unaffected (NCRP 1997b) so long as the errors are not correlated with radiation dose. Consequently, these errors are not an important factor in this analysis, which is based on relative risk models.

In contrast, misclassification errors do affect relative risk estimates for cancer mortality. This source of error has been investigated in some detail by RERF for the LSS data (Sposto et al. 1992). The overall crude misclassification rate for cancers was 22% and for noncancers was 3.5%. Sposto et al. (1992) determined that the excess relative risk at 1 Gy ( $ERR_{1Gy}$ ) for all cancers for a 50-year-old male exposed in Hiroshima at age 25 years should be increased by 13% to allow for this error. A sensitivity analysis showed that the  $ERR_{1Gy}$  for all cancer is essentially unchanged if the cancer misclassification rate is increased further from 22% to 33%.

For our analysis, the uncertainty in the bias in the risk estimate introduced by misclassification is accounted for with a multiplicative correction factor,  $f(M_i)$ . The central value of  $M$  for the combined category all cancers ( $M_{WB}$ ) is set at 1.13 based on the analyses of Sposto et al. (1992). A standard deviation of 0.08 is assigned where 95% of the values in the normal distribution range from 1.10 to 1.41.

Ron et al. (1994b) studied the agreement between death certificate and autopsy diagnoses for a subset of the LSS cohort. The misclassification rate for reporting cancer as noncancer for individual cancer sites was equal to or greater than that for the combined category of all cancers (24%). The observed misclassification rate for hematopoietic cancers was somewhat larger (32%) and larger still for liver (45%) and respiratory (46%) cancers. However, the categories hematopoietic cancers and respiratory cancers include more than leukemia and lung cancer, respectively. Data presented in Table III of Ron et al. (1994b) indicate that misclassification rates are greater for the combined categories than for the specific cancer site alone.

**Misclassification errors bias the risk estimates and occur when the cause of death is not identified accurately on a death certificate.**

Likewise, bone cancer is not reported separately but is grouped in the “other” category of neoplasms for the LSS data. The misclassification rate reported for this category was 53%.

Thompson et al. (1994), who studied liver cancer incidence in atomic bomb survivors, noted that the quality of diagnoses based on death certificate only is unacceptably poor, and 33% of the cases were identified by death certificate only. The effect of diagnostic accuracy on liver cancer incidence risk estimates was examined by evaluating the risk estimate according to the method of diagnosis (Table 6-7). The  $ERR_{1Sv}$ , based on histologically confirmed cases of liver cancer, was 35% greater than the value based on all reported liver cancer cases, indicating a very significant impact of misclassification on the risk estimate. The frequency with which liver cancer was confirmed histologically did not differ by dose. Assuming that the impact of misclassification on liver cancer mortality risk estimates is comparable to that on liver cancer incidence estimates, a large bias (1.35) is assigned. The standard deviation for the normal distribution is set at 0.135 and 95% of the values in the distribution range from 1.10 to 1.63.

The misclassification rate for leukemia is within the range examined by Sposto et al. (1992) in their sensitivity analysis; therefore, the same bias is assumed in the risk estimate as for the whole body, but with a slightly larger uncertainty. A larger bias (1.25) with considerable uncertainty is assumed for the lung to account for the increased misclassification rate seen for the combined category respiratory cancers. It does not seem appropriate to assume a value as large as for the liver. It is likely bone cancers are misclassified because bone is a preferred site for

metastasis of several common malignant tumors, such as cancers of the breast and prostate, themselves much more frequent than primary bone neoplasms (IARC 1993). The same bias and uncertainty are assigned to the bone as for the liver based on the similar misclassification rates reported in Table III of Ron et al. (1994b) and recognizing that it is grouped in the “other” category.

**Table 6-7. Liver Cancer Incidence Risk Estimates by Basis of Diagnosis**  
(taken from Thompson et al. 1994, Table XXXIV)

	Basis of diagnosis <sup>a</sup>			Total
	Histological	Visual-clinical	Death certificate only	
Number of cases	227	166	192	585
(% of total cases)	(39%)	(28%)	(33%)	(100%)
ERR <sub>ISV</sub>	0.66	0.41	0.36	0.49
(95% confidence interval)	(0.11–1.44)	(–0.14–1.27)	(–0.11–1.11)	(0.16–0.92)
Coefficient of variation	51%	88%	86%	39%

<sup>a</sup> Histological includes cytology; visual includes endoscopy and surgery; clinical includes X radiography and imaging.

Table 6-8 contains a summary of the statistical bias multipliers,  $f(M_i)$ , used to reflect the effect of misclassification of cancers on the risk estimates and described in the previous paragraphs. A normal distribution was used to model the uncertainty in each  $f(M_i)$ .

**Table 6-8. Summary of Statistical (Misclassification) Biases,  $f(M_i)$**

Cancer site	Distribution type	Distribution parameters <sup>a</sup>
Lung	Normal	$m = 1.25, s = 0.08$
Liver	Normal	$m = 1.35, s = 0.135$
Bone	Normal	$m = 1.35, s = 0.135$
Bone marrow (leukemia)	Normal	$m = 1.13, s = 0.05$
Whole body	Normal	$m = 1.13, s = 0.04$

<sup>a</sup>  $m$  = mean,  $s$  = standard deviation.

**6.3.1.3 Selection Bias.** The UNSCEAR (1994) lifetime mortality risk estimates are based on the LSS sample of 86,309 individuals for whom DS86 dosimetry is available for the follow-up period 1950–1987. If these subjects do not represent the general population, there will be a selection bias in the epidemiology that must be accounted for in the analysis. Potential limitations in the LSS cohort that have been noted include (a) fewer males between the ages 20 and 40 at the time of the bombing because of wartime service and (b) stress and food rationing due to wartime conditions. However, the LSS cohort is generally considered to be excellent compared with many other populations studied in epidemiology because it covers a good cross

section of normal people of all ages who received more or less whole body irradiation and a wide range of doses.

**Selection bias arises if the study subjects are unrepresentative of the source population.**

Because of the devastation caused by the blast and the trauma induced by bereavement, it is reasonable to assume that the surviving population may be to some extent fitter than the average. If this were the case, the radiation risk estimates for cancer and other health effects may in the short-term be less than for a normal, unselected population ([Little and Charles](#), 1990). However, [Kato et al.](#) (1981) had found no evidence for a selection effect. The potential also exists for the results to be internally biased if follow up of the survivors is selective. In the BEIR V report ([NAS/NRC](#) 1990), this is considered unlikely as follow up of the survivors to date has been virtually complete.

[Stewart and Kneale](#) (1990) have consistently argued that the Japanese bomb survivors are not representative of the population as a whole. They have developed a hypothesis that bias may have occurred due to the following two selection processes:

1. At the time of the bombing there was selection in favor of healthier, and, in particular, less radiosensitive people. The more radiosensitive people would be more likely to die shortly after the bombings from infectious diseases.
2. Damage to the immune system as a result of marrow damage occurred at higher doses.

Based on this hypothesis they argue that cancer mortality would exhibit a U-shaped dose-response where susceptibility to cancer initially decreases with dose and then, at higher doses, increases with dose as a result of damage to the immune system. Stewart and Kneale state that this effect has not been observed by other researchers because a linear model of relative risk is applied to the deaths of 5-yr survivors instead of a linear-quadratic model that they applied ([Stewart and Kneale](#) 1990).

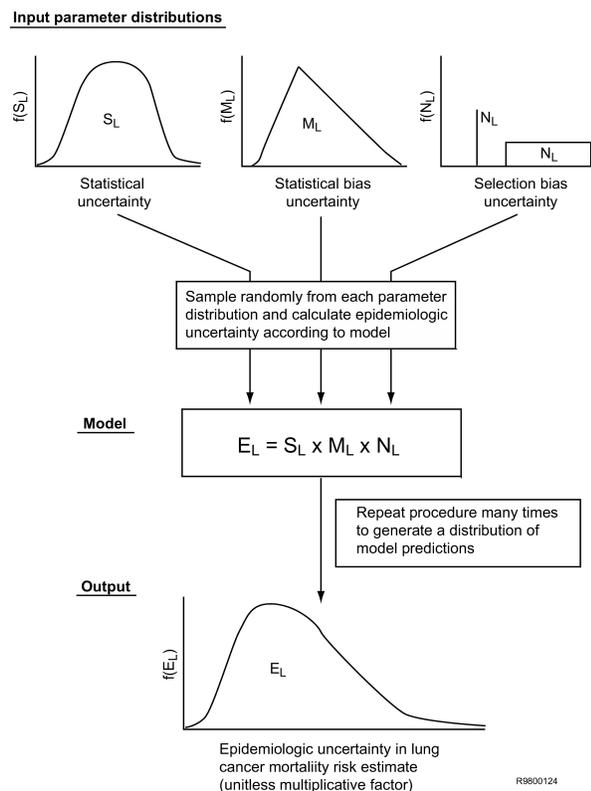
[Little and Charles](#) (1990) analyzed the health records of the Japanese bomb survivor population using both the older and newer dosimetry systems (T65D and DS86), and found some evidence for the selection effect hypothesized by Stewart and Kneale. This effect was found to be significant only in the first follow-up period examined (1950–1958), and it diminished in magnitude thereafter. In their analysis, Little and Charles state that the effect might be an artifact of the T65D dosimetry system because it is observed more strongly than in the data based on the DS86 dosimetry system. Little and Charles could find no evidence to support the assumption that selection on this basis confers correspondingly reduced susceptibility to radiation-induced cancer. Despite evidence to the contrary, Little and Charles proceeded to calculate the extent to which the current cancer risk coefficients would be underestimated if the Stewart and Kneale hypothesis is correct. They concluded that the risk coefficients could be underestimated by 5–35% at most and that the effect would diminish with time.

In our analysis the factor  $f(N_i)$  is used to represent the distribution of uncertainties potentially introduced by selecting a nonrepresentative cohort. The distribution is defined as follows. The probability that the risk coefficient is underestimated by anywhere between 5% and 35% is assigned 15%. Only a small probability is defined because the analysis in [Little and Charles](#) (1990) provides little support for such an effect. The more likely case appears to be that the study cohort, and therefore the risk coefficient, is unbiased, and this is assigned a probability of 85%. The same uncertainty in bias due to the nonrepresentative study cohort is assumed for specific cancer sites as for the whole body.

**6.3.1.4 Summary of Epidemiological Uncertainties.** Three sources of epidemiological uncertainty have been identified:

1. Statistical uncertainties
2. Statistical bias
3. Selection bias.

The three distributions reported in Tables 6-6, 6-8 and in the text, respectively, are combined to derive an overall distribution that represents the epidemiological uncertainties in the lifetime risk estimate for each organ (Figure 6-1). The percentiles of these distributions are presented in Table 6-9. All of the resulting distributions are approximately lognormal. The width of these distributions is indicated by the geometric standard deviation (GSD, see Glossary). The whole body and bone marrow distributions have the smallest GSDs (~1.2)<sup>g</sup>. The lung and liver distributions have GSDs of around 1.4, and the bone has the largest GSD (2.3). In all cases the 50th percentile values exceed 1.0 indicating that epidemiologic uncertainties tend to increase the risk estimates by 20–40% depending on the organ.



**Figure 6-1.** Procedure for determining the distribution of epidemiologic uncertainties in the cancer mortality risk coefficients for exposure to low-LET radiation using lung as an example.

<sup>g</sup> The  $GM \times GSD^2$  and the  $GM \div GSD^2$  define the range that is expected to include 95% of the distribution.

**Table 6-9. Epidemiological Uncertainty Distributions,  $f(E_i)$** 

Cancer site	Percentiles of distribution			
	2.5	50	97.5	GSD <sup>a</sup>
Lung	0.7	1.3	2.4	1.4
Liver	0.6	1.4	2.9	1.5
Bone	0.3	1.3	7.2	2.3
Bone marrow (leukemia)	0.7	1.2	1.7	1.3
Whole body	0.8	1.2	1.6	1.2

<sup>a</sup> GSD = geometric standard deviation of distribution (approximate).

### 6.3.2 Dosimetric Uncertainties

Estimating the dose received by every member of the LSS cohort is a fundamental component of determining the lifetime cancer mortality risk coefficients that are presented in [Section 6.2](#) and comprise the starting point for our assessment. Four sources of errors in the dosimetry have been identified which may impact the risk coefficients.

The first is random errors in the individual dose estimates resulting from incomplete information about the exact location and direction in which an individual was facing at the time of the bombing and the spatial precision of the models used to calculate the radiation fields. These random errors in the dose estimates cause systematic biases in estimates of risk based on a linear dose-response model, and also distort the shape of the dose response ([Pierce et al. 1990](#)). The net result is that the risk coefficients are negatively biased, i.e., underestimated.

The second is errors in estimating the magnitude of the fast neutron dose to individuals and the RBE of these neutrons. This information is required to determine the contribution fast neutrons make to the total equivalent dose received by individuals. The contribution of the neutrons to the dose in Hiroshima has been questioned and may be greater than in the DS86 dosimetry system especially at longer distances. This potential error and its impact on the risk coefficients has to be accounted for in the uncertainties.

The third is systematic errors in the gamma-ray field calculations for Hiroshima, which directly affect the dose estimates.

The fourth is possible errors in organ dosimetry because of the use of surrogate organs to estimate doses.

These sources of errors in the dosimetry, which bias the risk coefficients in different directions, are described in more detail below.

**6.3.2.1 Random Errors.** Random errors in individual dose estimates arise in part from errors in the input parameters used to compute doses. For example, individuals may not accurately recall their location relative to the hypocenter or the type of structure or terrain that was shielding them from the blast ([Sposto et al. 1991](#)). [Jablon \(1971\)](#) estimated that the uncertainties in a survivor's distance was between 47–62 m. For the estimated T65D dosimetry system doses, [Jablon \(1971\)](#) calculated the magnitude of these random errors (geometric standard deviation) to be 30–40%. In 1987 new dose estimates were calculated for the members of the LSS cohort using the DS86 dosimetry system, following growing concern over the accuracy of the T65D dosimetry system. However, this did not remove random errors due to survivor location and shielding uncertainties because the same basic input is required for the DS86 dosimetry system.

Random errors in the dosimetry lead to systematic bias in the estimated doses ([Pierce et al. 1990](#)) so that the estimated doses tend to be larger than the true values, and the risk is underestimated. Assuming a linear fit to the data these errors are greater in the high dose groups and distort the shape of the dose response (see [Section 6.3.5](#)).

Lifetime risk estimates for all cancers except leukemia were estimated using the DS86 dosimetry system in [Pierce et al. \(1990\)](#) and were found to be low by 10–16.7% in the 0–6 Gy range and by 6.8–11.4% in the 0–4 Gy range, assuming lognormally distributed 30–40% random errors in individual dose estimates. The corresponding values for leukemia were 6.1–10.2% (0–6 Gy range) and 4.3–7.2% (0–4 Gy). The range depends on the assumed magnitude of the lognormal errors in the individual dose estimates. Based on chromosome aberration data, [Sposto et al. \(1991\)](#) estimated that random errors in individual dose estimates are on the order of 45–50%, with an approximate 40% lower bound estimate. Assuming 45% lognormal random errors increases the lifetime risk estimates for all cancers except leukemia by about 13.5% and for leukemia by about 8.6% in the 0–4 Gy range. In their analysis, [Sposto et al. \(1991\)](#) assumed that random errors in dosimetry were the sole cause of differences in the data sets.

**The net result of random errors in the LSS dosimetry is that the risk estimates are negatively biased (underestimated).**

The bias in the risk coefficient introduced by random errors in dosimetry is accounted for using a multiplicative factor,  $f(dr_i)$ . The random dosimetry errors may range from about 30–45% in magnitude, which increases the risk estimate for solid tumors by 6–14% and leukemia by 4–9%. It is assumed that there is the same range in bias for whole body as for solid tumors. Because there is little information available about the nature of the distribution of the uncertainties in the bias, a triangular distribution is assumed that defines the most likely value and the probable range of values. Furthermore, the uncertainty in the bias for lung, liver, and bone risk estimates is assumed to be the same as the overall category, solid tumors, of which they are a part. [Table 6-10](#) summarizes the distributions used in our analysis.

**6.3.2.2 Systematic Errors.** Systematic errors may arise in the individual dose estimates because of the possible presence of more fast neutrons at Hiroshima than estimated in the DS86 dosimetry system ([Straume et al. 1992](#)). In addition, [UNSCEAR \(1994\)](#) points out that a reanalysis of chromosome aberration data for the Japanese survivors places the neutron

**Systematic errors have been identified in the DS86 dosimetry system for the neutron doses and the gamma ray field calculations for survivors in Hiroshima. Both cause the risk estimates to be positively biased (overestimated).**

component at about 5% of the absorbed dose for Hiroshima compared with about 1–2% in the DS86 dosimetry system ([Sasaki et al. 1992](#)). Thus, there is evidence that the DS86 dosimetry system may significantly underestimate the neutron doses to the Hiroshima survivors and the relative magnitude of the error increases with distance from the hypocenter, which gives rise to a systematic bias in the dosimetry. The increased numbers of fast

neutrons do not introduce large uncertainties into the dose and risk estimates because the errors are not large in the dose categories that contribute most to risk. According to [Preston et al. \(1992–1993\)](#), the upper limit for the bias in the risk coefficient for all cancers except leukemia because of the presence of more fast neutrons at Hiroshima is a decrease of about 22% assuming a neutron RBE of 20. If a smaller RBE value is selected, there is a smaller decrease in the risk estimate (~13% decrease for an RBE of 10). However, some authors ([Straume 1996a](#); [Rossi and](#)

[Zaider](#) 1996) maintain that the effect of additional neutrons on the risk coefficient at low doses is much greater, although their arguments are countered by researchers at RERF ([Pierce et al.](#) 1996b). A newly proposed technique for measuring fast neutrons directly in copper ([Straume](#) 1996b) may eventually resolve the magnitude of the neutron component at Hiroshima.

An additional uncertainty is in the assignment of an RBE to neutrons. [Shimizu et al.](#) (1989) examined the change in risk coefficients for the DS86 dosimetry system if a neutron RBE value of 10 or 20 is selected rather than 1. The smallest difference was seen for the combined category of all cancers except leukemia where the median risk estimate decreased by 7% and 13%, respectively. Larger differences were observed for specific cancer sites. The median risk estimate (per sievert) for leukemia decreased by 10% and 19% assuming an RBE of 10 and 20, respectively, compared to an RBE of 1. For lung cancer the corresponding decreases in the median risk estimate were 12% and 22%, respectively. Even though the risk estimates do not vary greatly with the assumed RBE value, [UNSCEAR](#) (1994) states that preference should be given to estimates based on values of 10 to 20. Currently, a neutron RBE of 10 is generally used in analyses of the atomic bomb survivor data. Indeed, this was the case for the [UNSCEAR](#) (1994) lifetime risk coefficients that provide the basis for our analysis.

In our analysis, the uncertainty in the bias in the risk coefficient introduced by systematic errors in the individual neutron dosimetry and uncertainty in the neutron RBE is represented by  $f(ds_i)$ , a multiplicative correction factor. For the category whole body, a central estimate of 0.85 is assumed for this factor based on the 13% decrease in the risk coefficient for all cancers except leukemia observed in the RERF study, which assumed a neutron RBE of 10. Given the uncertainty in the neutron RBE value and the neutron component of the absorbed dose for Hiroshima, a range from 0.75 to 0.95 with a triangular distribution is assumed ([Table 6-10](#)). For the individual cancer sites, the decrease in the risk coefficient is assumed to be somewhat greater based on the larger decreases in the risk coefficients observed by [Shimizu et al.](#) (1989).

Another source of systematic error that has been identified for the DS86 dosimetry system, is in the gamma ray field at Hiroshima at the time of the bombing. Comparison of thermoluminescent dosimeter measurements of ceramic bricks exposed at the time of the bombing with the gamma ray fields that are estimated for the DS86 dosimetry system using transport models, indicates that the true value may be systematically underestimated and that the bias increases with distance from the hypocenter ([Maruyama et al.](#) 1987). It is reported ([NCRP](#) 1997b) that correcting for this systematic error changes the doses near the hypocenter very little but increases them by approximately 20% at 1000 meters. This systematic error does not appear to apply to the Nagasaki gamma-ray field that is estimated using the DS86 dosimetry system. In our analysis, the uncertainty in the bias in risk coefficients introduced by bias in the dose estimates arising from systematic errors in the gamma-ray fields is represented by  $f(dg_i)$ , a multiplicative dose correction factor. These values are the reciprocal of the uncertainties in the dose estimates because risk is expressed per unit dose. The triangular distribution that results for the uncertainties in the dose estimates has a most probable value of 1.1, with a lower bound of 1.0 and an upper bound of 1.4. Therefore, the corresponding triangular distribution that is used to account for the uncertainties in the risk coefficients has a most probable value of 0.9, and ranges from 0.7 to 1.0.

**6.3.2.3 Organ Dosimetry Errors.** Although in the LSS and the DS86 dosimetry system all the main organs are treated directly, sometimes surrogate organs are used. The most notable example is the use of intestinal dose for whole body dose as the basis of risk coefficients. Errors

of the order of 6–10% could arise from this source (NCRP 1997b) although an actual example comparing whole body risk using intestinal dose with whole body risk summing all twelve ICRP organs and remainder at 1200m (Hiroshima) realized an error of only 0.4%. In any case, in this report, although we include whole body risk coefficients, the main focus is on the risk to the lung, liver, bone and bone marrow. For these organs, doses are directly available from DS86. Therefore no additional uncertainty from this source is included in the summary table.

**6.3.2.4 Summary of Dosimetric Uncertainties.** Table 6-10 summarizes the dosimetric uncertainty factors due to random and systematic errors. The three distributions were combined using the methodology shown in Figure 6-1 for the epidemiologic uncertainties. Table 6-11 presents the overall uncertainty distribution that results from combining these components. All three distributions are approximately normal with about 10% coefficient of variation.

**Table 6-10. Summary of Dosimetric Uncertainty Factors,  $f(dr_i)$ ,  $f(ds_i)$  and  $f(dg_i)$**

Cancer site	Distribution parameters <sup>a</sup>		
	Random errors	Systematic errors	
	$f(dr_i)$ (location and shielding)	$f(ds_i)$ (neutron dose)	$f(dg_i)$ (gamma ray field)
Lung, liver, or bone	Triangular a = 1.03; b = 1.10; c = 1.17	Triangular a = 0.70; b = 0.80; c = 0.95	Triangular a = 0.7; b = 0.9; c = 1.0
Bone marrow (leukemia)	Triangular a = 1.02; b = 1.07; c = 1.11	Triangular a = 0.70; b = 0.80; c = 0.95	Triangular a = 0.7; b = 0.9; c = 1.0
Whole body	Triangular a = 1.03; b = 1.10; c = 1.17	Triangular a = 0.75; b = 0.85; c = 0.95	Triangular a = 0.7; b = 0.9; c = 1.0

<sup>a</sup> a = lower bound, b = most probable value (mode), c = upper bound.

**Table 6-11. Combined Dosimetric Uncertainty  
Factor Distributions,  $f(D_i)$**

Cancer site	Percentiles of distribution		
	2.5	50	97.5
Lung, liver, bone	0.63	0.78	0.93
Bone marrow (leukemia)	0.62	0.75	0.90
Whole body	0.67	0.81	0.94

### 6.3.3 Uncertainties in Projection to Lifetime Risks

Current estimates of lifetime risk are based on the LSS population, of which approximately 60% were still living at the end of the evaluation period in 1987. Models are required to

extrapolate beyond the time period covered by the observed population to the lifetime of the entire population, especially for persons whose exposure occurred at an early age.

Different lifetime risk projection models have been used and time-constant ERR models have been identified as the most useful simple description of the data at the present time. The LSS data exhibit a steady increase in excess absolute risk for solid tumors for any given gender and age at exposure in 1945. These data closely mirror the increase in background cancer rate for a given gender and age at exposure. However, [UNSCEAR](#) (1994) questions the adequacy of the time-constant excess relative risk model in view of the dependence of excess relative risks on age at exposure. The key issue is the projection for those exposed as children who are only now attaining ages at which the background rates of cancer become significant. [UNSCEAR](#) (1994) provided two alternative projection scenarios that reduce the population-weighted lifetime risk of mortality from solid tumors by up to 16–32% over that based on a constant relative risk projection. In these two models, it is assumed that for those survivors who were less than 45 years old at exposure, the excess relative risk begins 5 years after exposure, is constant for 40 years, and then either declines to an intermediate level (equivalent to the average excess relative risk for a survivor who was 50 years old at exposure) or to zero excess relative risk at age 90. Using these two approaches, the differences are most pronounced in the youngest age groups (newborn to 5 years old at exposure) where the lifetime risk estimate decreases by up to 30–52% over that based on a constant relative risk projection (based on Table 30, [UNSCEAR](#) 1994). For

**Lifetime risk projection models are required to extrapolate beyond the time period covered by the observed population to the lifetime of the entire population.**

exposures occurring between ages of 5 and 20 years, the lifetime risk estimate decreases by up to 12–45%. For exposures occurring between ages greater than 20 years and less than 50 years, the lifetime risk estimate decreases by 0–30%. The choice of risk projection model has no impact for individuals who were 50 years old or greater at exposure. The evidence from the analysis by [Pierce et al.](#) (1996a) of the atomic bomb survivors, which includes the follow-up period 1986–1990, supports a decrease with time in the nonleukemia cancer mortality for the youngest survivors. Analysis of the solid tumor incidence data ([Thompson et al.](#) 1994) leads to a similar conclusion. [Little et al.](#) (1991) have also concluded that there is evidence of a decrease with time in the excess relative risk for solid tumors following childhood exposure.

Time-increasing EAR models ([Kellerer and Barclay](#) 1992; [Pierce and Preston](#) 1993) can describe the present LSS data almost as well as the time-constant ERR models described above. The model developed in [Kellerer and Barclay](#) (1992) allows the excess absolute risk to decrease with increasing attained age without any additional dependence on age at exposure. If this or some other alternative model is more appropriate than the constant excess relative risk model, the current risk estimates (which are based on the latter) will be overprojected by perhaps as much as a factor of 2. There appears to be consensus that time-constant absolute risk models do not fit the current data and are no longer useful for projecting risk ([UNSCEAR](#) 1994).

It is assumed that there is no uncertainty in the leukemia risk estimates as a result of risk projection because essentially all excess leukemias have been observed, removing the necessity for risk projection ( $f[P_{LK}] = 1.0$ ). However, there are insufficient data to determine the uncertainty associated with risk projection for each specific cancer type (i.e., lung, liver, bone). For this reason, the uncertainty in the lifetime risk estimate associated with the choice of risk-projection model is based on the observed differences in the total solid tumor mortality and is

accounted for by a multiplicative factor,  $f(P_i)$ . Allowance is made for the possibility that the constant relative risk model underestimates the lifetime risk for all cancers although this is not considered very likely. Therefore, the upper estimate for the distribution of  $f(P_i)$  is set at 1.1, 10% higher than the current value. It is considered unlikely that the alternative projection model developed by [Kellerer and Barclay](#) (1992), or some variation, could overestimate the lifetime risk for all cancers; therefore, the lower estimate of the range is set at 0.5. The most probable value is set at 0.85, assuming that the nominal lifetime risk value overestimates the real risk by 15% because the ERR may decline with time eventually. Table 6-12 summarizes these distributions.

**Table 6-12. Summary of Projection to Lifetime Risk Uncertainties,  $f(P_i)$**

Cancer site	Distribution type	Distribution parameters <sup>a</sup>
Lung, liver, bone	Triangular	a = 0.5, b = 0.85, c = 1.1
Bone marrow (leukemia)	No uncertainty assumed	a = b = c = 1.0
Whole body	Triangular	a = 0.5, b = 0.85, c = 1.1

<sup>a</sup> a = lower bound, b = most probable value (mode), c = upper bound.

### 6.3.4 Uncertainties in Transfer of Risk from a Japanese to a U.S. Population

Considerable uncertainty is associated with extrapolating risk estimates to a population other than the one for which they were derived. Although different populations may have quite similar total cancer rates, they often have very different site-specific cancer rates, and these rates change with time. Not only does the present day Japanese population differ from the U.S. population, but also the characteristics of the Japanese population in 1945 differ from those of the present day. Currently, there is no clear indication of how best to transfer risk estimates to different populations ([UNSCEAR](#) 1994; [Land and Sinclair](#) 1991). [Leenhouts and Chadwick](#) (1994) have considered these transfer questions and discussed models that could apply. Two models have been used in [Land and Sinclair](#) (1991) to handle this situation but there are few tests of these two alternatives.

**Even though different populations have similar total cancer rates, they often have very different site-specific cancer rates.**

1. A multiplicative transfer model where the relative risk in the exposed population is transferred to the new population using the spontaneous risk in the new population as the base.
2. An additive transfer model (National Institutes of Health [NIH] model) where the absolute values of risk in the Japanese population are transferred to the new population without reference to the spontaneous rates of cancer in the new population.

The ICRP applied both models to five populations (Japan, U.S., Puerto Rico, United Kingdom, and China) to calculate the risks for total cancer and then took the average to minimize the potential error from this source. The largest differences in lifetime risk estimates for total cancer occurred if the multiplicative model was applied. These varied at most by a factor of 2 and by only 30% if the Chinese population was excluded.

The [EPA](#) (1994) carried out an analysis using a Monte Carlo procedure to select randomly from either the multiplicative or NIH projection models for each organ before summing over all organs to calculate the total lifetime risk. Using this technique, the mean lifetime risk estimate is about 10% higher than the nominal value, and the coefficient of variation is about 20% higher. This re-analysis confirms the ICRP results.

**There is considerable uncertainty about the correct method for transferring risk estimates obtained from one population to another.**

For our analysis we are interested in the transfer of risk for individual organs. Using the data from [Land and Sinclair](#) (1991), the relative probabilities of fatal cancer in organs are presented in Table 6-13. The U.S. population is compared with the Japanese population using both the multiplicative and NIH models to transfer the risks. For lung cancer these vary by up to 45% and for leukemia by up to 20%. Differences in the baseline cancer mortality rates between the U.S. and Japanese populations for these two sites explain the large variation in the projected cancer risks; both lung cancer and leukemia are more prevalent in the U.S. Other factors, such as all-cause mortality rate, age distributions, and expected life spans also contribute to the differences in the baseline cancer mortality rates ([Land and Sinclair](#) 1991).

**Table 6-13. Relative Probabilities of Fatal Cancer in Organs for a U.S. and Japanese Population Determined Using Two Projection Models<sup>a</sup>**

Organ	Multiplicative		NIH	
	Japanese	U.S.	Japanese	U.S.
Oesophagus	0.038	0.014	0.042	0.025
Stomach	0.291	0.033	0.268	0.317
Colon	0.180	0.320	0.121	0.188
Lung	0.174	0.205	0.221	0.121
Breast	0.023	0.075	0.027	0.034
Ovary	0.014	0.031	0.019	0.023
Bladder	0.052	0.076	0.052	0.048
Bone marrow (leukemia)	0.077	0.096	0.100	0.093
Remainder	0.150	0.150	0.150	0.150
All cancer	0.999	1.000	0.998	0.999
Total probability ( $10^{-2} \text{ Sv}^{-1}$ )	10.7	11.2	9.7	8.7

<sup>a</sup> Exposed to 1 Sv acute radiation: average of male and female, age 0–90 years; based on Table 5, [Land and Sinclair](#) (1991); Tables B–14A and B–14B, [ICRP](#) (1991).

The analysis of [Land and Sinclair](#) (1991) provides no information about liver and bone cancers. At the time of their analysis, these sites fell into the “remainder” category, which was set to 15% for both genders and all exposure ages, populations, and projection models. The baseline bone cancer mortality rates in Japan and U.S. are similar: 1 per 100,000 or less ([IARC](#) 1993). This suggests that the difference between the multiplicative and NIH projection models in transferring the risk would not be as large as for lung and leukemia. Based on this information, in our analysis a 20% coefficient of variation is assumed for the uncertainty in risk transfer for bone. In the U.S. the annual baseline liver cancer mortality rate is about one-half that for

leukemia: 3.2 per 100,000 versus 6.4 per 100,000 ([NCI 1995](#)). The background rate of liver cancer in Japan is high ([Pierce et al. 1996a](#)) therefore a large (80%) coefficient of variation is assumed for the transfer uncertainties for liver.

The uncertainty in the whole body cancer risk estimate resulting from transferring the risk from the Japanese population to a U.S. population is represented by the parameter  $f(T_{WB})$ , which is described using a normal distribution with a mean of 1 and a standard deviation of 0.15. The uncertainties for the individual organ risk estimates are larger. The uncertainty in the bone cancer risk estimate is modeled using a normal distribution with a mean of 1 and a standard deviation of 0.2. The uncertainties for the lung, liver and bone marrow cancer risk estimates are modeled using lognormal distributions. This avoids the potential selection of negative numbers that can occur when a normal distribution with a large coefficient of variation is assumed. A GM of 1 is assigned to each lognormal distribution. The GSD for the lognormal distribution is calculated so that it yields approximately the same standard deviation as the normal distribution from which the data are derived. The values are summarized in Table 6-14.

**Table 6-14. Summary of Uncertainties Associated with Transfer from a Japanese to a U.S. Population,  $f(T_i)$**

Cancer site	Distribution type	Distribution parameters <sup>a</sup>
Lung	Lognormal	GM = 1.0, GSD = 1.49
Liver	Lognormal	GM = 1.0, GSD = 1.78
Bone	Normal	m = 1.0, s = 0.20
Bone marrow (leukemia)	Lognormal	GM = 1.0, GSD = 1.27
Whole body	Normal	m = 1.0, s = 0.15

<sup>a</sup> GM = geometric mean, GSD = geometric standard deviation, m = mean, s = standard deviation.

### 6.3.5 Uncertainty in the Dose and Dose Rate Effectiveness Factor and the Dose Response for Low-LET Radiation

The data from the survivors of the atomic bombings in Japan essentially relate to a single dose of low-LET radiation given at a high dose rate. Nearly all environmental radiation doses are delivered over much longer time periods at a much lower dose rate. The doses at Rocky Flats fall into this category. Many studies show a reduced incidence of cancer at low dose rates when compared with high dose rates ([Sinclair 1993b](#)). Similarly, many radiobiological phenomena involving low-LET radiations show reduced effectiveness for low dose rates as compared with high dose rates. Based on such data, [ICRP \(1991\)](#) recommends a DDREF of 2. Although the NCRP accepts this value, a larger value 2–3 would have been preferred. [UNSCEAR \(1993\)](#) reevaluated this whole situation in its Annex F and recommended that a DDREF not greater than 3 be used for doses below 200 mGy and dose rates less than 0.1 mGy min<sup>-1</sup>.

Ninety percent of the total risk in the atomic bomb survivors is due to solid tumors ([Sinclair 1993b](#)), and the dose response curve for these is best fit with a linear curve. [Pierce and Vaeth \(1991\)](#) analyzed the LSS mortality data, adjusting for dosimetry errors, and determined a DDREF of 1.3 for solid tumors with an upper 95% confidence bound of 3.6. A 35% coefficient of variation in dose errors was assumed. In a similar analysis of the incidence data reported in [UNSCEAR \(1994\)](#), [Vaeth et al. \(1992\)](#) estimated a DDREF for solid tumors of about 1.05 with a

90% confidence interval of about 0.6 to 1.6. These values contrast with the higher values noted earlier. A possible explanation has been offered by Sinclair, who demonstrated that a linear quadratic dose response model is not incompatible with the LSS observations if a cell-killing term is introduced into the equation (Sinclair 1993b). This notion is supported by a recent analysis of the low dose region (<0.5 Sv) of the LSS data (Shimizu et al. 1993). A linear dose response with a lower gradient was obtained for the range 0–0.5 Sv, compared with the result when all data for doses less than 4.0 Sv were analyzed.

In their analysis of the LSS mortality data with adjustment for dosimetry errors, Pierce and Vaeth (1991) also determined that the DDREF for leukemia is likely to be larger than for solid tumors. Assuming a 35% coefficient of variation in the dosimetry errors, they obtained a DDREF of approximately 1.8 for leukemia and an upper 95% confidence bound of about 6.0. In the BEIR V report (NAS/NRC 1990), a best estimate DDREF value of 2 was determined for leukemia based on the atomic bomb survivors. According to EPA (1994), current scientific data support a

**The concept of a DDREF and its magnitude is inseparable from the question of the shape of the dose-response curve.**

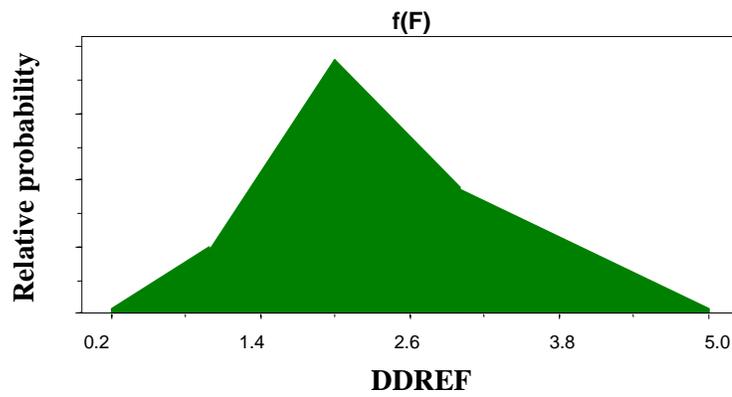
DDREF between 1 and 3 for human cancer induction.

The concept of a DDREF and its value is inseparable from the question of the shape of the dose response itself (NCRP 1980; UNSCEAR 1994). See Figure 6-4 and Section 6.4.3. Assigning a value of 2 to the DDREF is equivalent to describing a linear quadratic dose response in which the initial linear portion has a slope only one-half of the slope of a simple linear dose response function extrapolated to the origin. As will be explained in the following paragraphs, the uncertainty assigned in our analysis to the DDREF (value = 2) is from 0.2 to 5. This allows the initial dose response to range from a slope greater than one to one-fifth of a simple linear dose response function. This range is broad enough to account for initial forms of response different from linear within this range. Thus, no new uncertainty is introduced by the dose response assumption over that already assigned to the DDREF itself, unless zero risk in the low-dose region is considered a real possibility. While some may espouse zero risk, the authors of this report consider a continuous risk in the low-dose region to be much the more likely form of response (see Section 4.11.9).

Although the LSS dose response curve for solid tumors is remarkably linear, it is important to remember that it is a composite of response curves for many solid tumors. There is some evidence that different tumor sites have different dose response curve shapes. Clinical studies of radiation-induced breast and thyroid cancer show that dose fractionation makes little or no difference to the risk compared with acute dose, whereas other studies for the lung indicate that the difference can be large. A study by Howe (Howe 1995) of lung cancer mortality after exposure to fractionated, moderate dose-rate ionizing radiation ( $\sim 0.6 \text{ mGy s}^{-1}$ ) in the Canadian fluoroscopy cohort study showed a substantial fractionation/dose-rate effect for low-LET radiation and lung cancer risk. In that study, no ERR of lung cancer mortality was observed. However, for the atomic bomb survivors who were also exposed to low-LET radiation that was delivered almost instantaneously at a high dose rate ( $\sim 240 \text{ mGy s}^{-1}$ ), an ERR of 0.6 (95% CI = 0.26–0.99) was observed. Using the results presented in Howe (1995), a DDREF of about 8 for lung cancer induction can be determined for extrapolating from acute, high dose-rate exposures to fractionated, moderate dose-rate exposures to low-LET radiation. Given that the dose rate in the Canadian fluoroscopy cohort study is still somewhat larger than the value suggested by UNSCEAR (1994) ( $<0.1 \text{ mGy min}^{-1}$ ) to distinguish low dose rates, a somewhat larger DDREF may be anticipated for fractionated exposures. Despite this, analysis of lung cancer incidence in

the atomic bomb survivors demonstrates a strong linear dose response with no evidence of nonlinearity ([Thompson et al. 1994](#)) such as might be expected if fractionation is likely to reduce the effect.

In summary, a best estimate value of 2 based on the analysis by [Pierce and Vaeth \(1991\)](#), is used to describe the distribution of uncertainties in the DDREF,  $f(F_{WB})$ , for all cancers. The lower bound value for the distribution is set at 0.2 and the upper bound estimate at 5. A modified triangular distribution is used to describe  $f(F_{WB})$ , where the probability of a value of one for the DDREF is one-quarter that for the best estimate. The probability of a value of three equals one-half that for the best estimate (see Figure 6-2). The lower limit for the DDREF is set at 0.2 to account for the possibility of supralinearity in the dose-response curve (see [Section 4.11.6](#)). The uncertainty in the shape of the dose response is included in this estimate.



**Figure 6-2.** Uncertainty distribution of the DDREF for the whole body, liver, and bone.

The data suggest that the distribution of uncertainties in the DDREF for lung is different from total cancer and that there is evidence of a more pronounced effect of DDREF. Consequently, a best estimate of 4 is assumed with the upper bound estimate set at 10. Again the lower limit for the DDREF is set at 0.2 to account for the possibility of supralinearity in the dose-response curve. The probability of a value of one for the DDREF is set at one-quarter that for the best estimate value of 4.

No information is available to allow us to discriminate liver cancer and bone cancer from all cancers; therefore, it is assumed that the distribution of uncertainties is the same as for the whole body. For leukemia, the distribution of uncertainties in the DDREF is based on the analysis by [Pierce and Vaeth \(1991\)](#). A best estimate of 2 is assumed and the lower bound estimate is set at 1 because there is no evidence of supralinearity in the dose response, and the upper bound estimate is set at 7. A log-triangular distribution is used to describe this factor,  $f(F_{LK})$ . The distributions assumed for this factor in the uncertainty modeling are shown in [Table 6-15](#).

**Table 6-15. Summary of Uncertainty Distributions for DDREF,  $f(F_i)$** 

Cancer site	Distribution type	Distribution parameters <sup>a</sup>
Lung	Modified triangular <sup>b</sup>	$a = 0.2, b = 4, c = 10$
Liver	Modified triangular <sup>c</sup>	$a = 0.2, b = 2, c = 5$
Bone	Modified triangular <sup>c</sup>	$a = 0.2, b = 2, c = 5$
Bone marrow (leukemia)	Log triangular	$a = \ln 1, b = \ln 2, c = \ln 7$
Whole body	Modified triangular <sup>c</sup>	$a = 0.2, b = 2, c = 5$

<sup>a</sup> a = lower bound, b = most probable value (mode), c = upper bound, ln = natural logarithm.  
<sup>b</sup> See text for explanation.  
<sup>c</sup> See [Figure 6-2](#).

### 6.3.6 Calculation of the Low-LET Lifetime Risk Coefficients of Cancer Mortality for the U.S. Population

Lifetime risk coefficients of cancer mortality for exposure to low-LET radiation ( $R_{USi}$ ) are calculated for the U.S. population using the lifetime risk coefficients determined for the Japanese bomb survivors (LSS cohort). As noted earlier (Sections [6.2](#) and [6.3.2.2](#)), these risk estimates are reported on a percent per sievert basis because an RBE value is generally assumed for the neutron dose component which contributes only a small fraction of the total absorbed dose. However, because the risk estimates are primarily for exposure to low-LET gamma radiation, it is assumed that the reported risk per sievert is equal to the risk per gray.

These risk coefficients are presented in [Table 6-4](#) and provide the starting point for our analysis. The various factors that contribute to uncertainty and bias in these risk coefficients are included in the analysis as unitless multiplicative factors. In this way the relative uncertainty or bias associated with each factor is accounted for in the calculation. Information about the relative distribution of these uncertainties is incorporated by specifying the appropriate distribution function, for example, normal distribution, lognormal distribution, and triangular.

The estimated lifetime risk coefficient of cancer death for a U.S. population exposed to low-LET radiation ( $R_{USi}$ ) received in low doses at a low dose rate is calculated, using a Monte Carlo random sampling technique, according to the following equation.

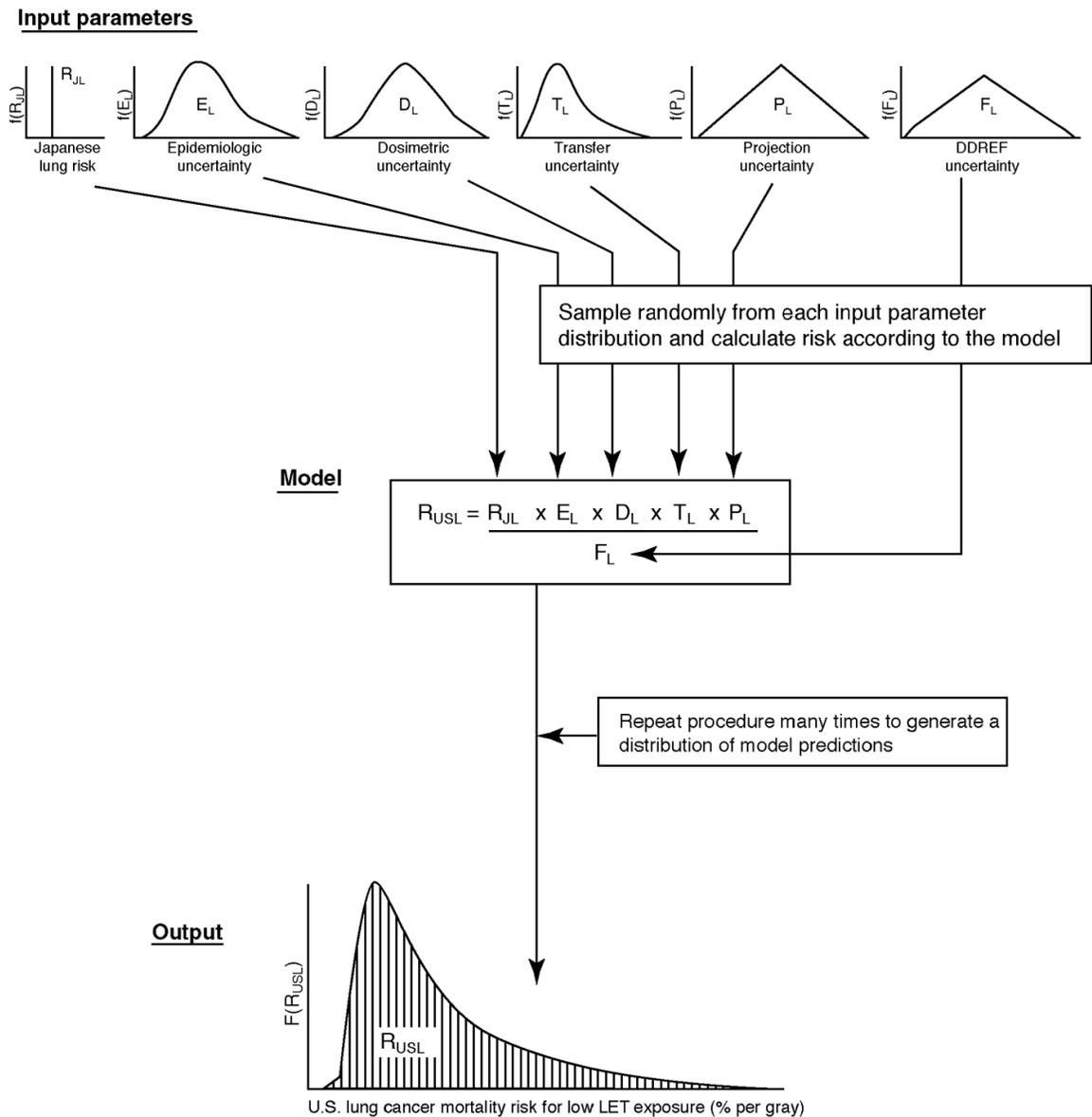
$$R_{USi} = [R_{ji} \times f(E_i) \times f(D_i) \times f(T_i) \times f(P_i)] \times f(F_i)^{-1} \quad (6-1)$$

where i represents the cancer site of interest: L = lung, LV = liver, B = bone, LK = leukemia, and WB = for total cancer (whole body). Other variables in the equation are

- $R_{ji}$  = low-LET lifetime risk coefficient of excess cancer death (Japanese data) presented in [Table 6-4](#) (% per Gy)
- $f(E_i)$  = epidemiological uncertainties (unitless)
- $f(D_i)$  = uncertainties due to dosimetry errors (unitless)
- $f(T_i)$  = uncertainty in transfer of risk to a U.S. population (unitless)
- $f(P_i)$  = uncertainty in the projection to lifetime (unitless)
- $f(F_i)$  = uncertainty in the DDREF and dose response relationship (unitless).

For each cancer site of interest, a total of 10,000 iterations were made using the Monte Carlo sampling technique to establish the distribution of  $R_{USi}$ . It was assumed that there are no

correlations between any of the parameters included in the uncertainty analysis. The entire procedure is represented schematically in Figure 6-3 taking lung as an example.



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**Figure 6-3.** Procedure for combining uncertainties in input parameters to determine cancer mortality risk distribution for exposure to low-LET radiations using lung as an example.

[Table 6-16](#) summarizes the output distributions for the resulting lifetime risk of fatal cancer. In each case the distribution is approximated by a lognormal distribution. The smallest uncertainties are associated with the whole body and bone marrow (leukemia). These range by about a factor of 2 to 3 in either direction of the median estimate. The lung and liver risk coefficients vary by about a factor of 5 in either direction of the median estimate. The largest uncertainty is associated with the bone risk coefficient, and this varies from the median estimate

by a factor of 6 to 8 in either direction. The median estimates differ significantly from the nominal values used by [ICRP](#) (1991) because of the different factors that have been accounted for and described in the text.

**Table 6-16. Summary of Lifetime Fatal Cancer Risk Coefficients ( $10^{-2}$  Gy $^{-1}$ ) for a U.S. Population Exposed to Low-Dose, Low-LET Radiation**

Cancer site	Lifetime risk coefficient distribution percentiles		
	2.5	50	97.5
Lung	0.10	0.37	2.0
Liver	0.076	0.39	2.1
Bone	0.002	0.012	0.094
Bone marrow (leukemia)	0.14	0.40	1.1
Whole body	1.6	3.9	13

The uncertainty in the whole body low-LET risk coefficient can be compared with the uncertainty estimates determined by [NCRP](#) (1997b) and [EPA](#) (1995). To do this the low-LET risk coefficient was recalculated using the same nominal lifetime risk coefficient for low-LET exposure at high dose-rates as used by both the NCRP and the EPA, i.e.,  $10 \times 10^{-2}$  Gy $^{-1}$  rather than the  $12 \times 10^{-2}$  Gy $^{-1}$  that we had determined based solely on the Japanese population (see [Section 6.2](#)). For this reason the median lifetime risk estimate from the present analysis is lower than that presented in [Table 6-16](#). Furthermore, the 5th and 95th percentiles of the output distributions are presented in [Table 6-17](#) to allow direct comparison with those reported by NCRP and EPA. All the risk coefficients are uncertain by about a factor of 2 to 3 in either direction of the median value. The median EPA risk estimate is somewhat higher than the other two, but all three distributions are similar.

**Table 6-17. Comparison of Whole-Body, Low-LET, Low-Dose Lifetime Fatal Cancer Risk Coefficients ( $10^{-2}$  Gy $^{-1}$ )**

Origin of risk estimate	Lifetime risk coefficient distribution percentiles		
	5	50	95
<a href="#">NCRP</a> (1997b)	1.2	3.4	8.8
<a href="#">EPA</a> (1995)	2.0	4.5	9.9
Present analysis <sup>a</sup>	1.5	3.3	8.3

<sup>a</sup> Based on an acute exposure risk of  $10 \times 10^{-2}$  Gy $^{-1}$  and not  $12 \times 10^{-2}$  Gy $^{-1}$

## 6.4 Relative Biological Effectiveness of Alpha Particles

To estimate the plutonium risk based on low-LET risk estimates derived from the LSS of atomic bomb survivors, appropriate values of the RBE for plutonium alpha particles must be used to obtain the risk per unit equivalent dose. The ICRP ([ICRP 1991](#)) and NCRP ([NCRP 1993a](#)) recommend 20 for the value of the radiation weighting factor,  $w_R$ , a “legislated” RBE (see [Section 6.4.4](#)) for all radiation protection circumstances involving alpha emitters. However, this general recommendation may not be appropriate for very specific circumstances such as determining the risk from the effects of plutonium in individual tissues. In this part of the report, each organ of interest is considered individually to determine the most appropriate RBE value, the range of RBE values, and the uncertainties involved in each case.

### 6.4.1 Background on Developing RBEs

When the absorbed dose (a measure of the energy imparted to the medium) was first defined, many hoped that the biological response would be the same for all absorbed doses. This was quickly found not to be the case. In addition to the amount of energy deposited in tissue, the way in which it was deposited was also found to be important and influence effectiveness. High-LET particles (alphas and neutrons) cause densely ionizing tracks in tissue and are usually more effective per unit absorbed dose than low-LET radiations with only sparsely ionizing tracks. High-LET particles are said to have a greater RBE with respect to low-LET radiation as a standard.

The RBE itself is defined as the absorbed dose of the standard radiation divided by the absorbed dose of the test radiation for the same (chosen) level of biological effect. Typically, RBE values will vary with the system being studied and the endpoint. In radiobiological work it is usual to account for and specify such differences. It is also usual in radiobiology to use a specific standard radiation such as gamma rays because gamma rays not only have the lowest LET (about  $0.3 \text{ keV } \mu\text{m}^{-1}$ ), but they are also the principal radiation involved in the atomic bombs dropped at Hiroshima and Nagasaki from which the principal low-LET risk is derived. X-rays are often taken as equivalent to gamma rays as a standard for radiation protection ([ICRP 1991](#); [NCRP 1993a](#)). However, in more precise risk estimation circumstances, it is recognized that at low doses x-rays (50–250 kVp) are about 2 or 3 times more effective than gamma rays ([Bond et al. 1978](#); [ICRU 1986](#); [Sinclair 1985](#)). High energy electrons, such as those from many beta-emitting radionuclides, are similar in LET and biological effectiveness to gamma rays.

**High-LET particles (alphas and neutrons) usually have a greater biological effect per unit absorbed dose than low-LET radiations (gamma rays).**

### 6.4.2 Earlier Evaluations of Alpha Particle RBEs

The RBEs of alpha particles (and some other radiations such as fission neutrons) have been widely studied in a variety of different organisms and endpoints. The ICRP and NCRP, in putting together this information some decades ago (1950s to 1970s), used the number of ion pairs produced and specific ionization to describe the dependence of the RBE on energy deposition. The dependence is shown in [Table 6-18](#) ([NCRP 1954](#); [ICRP 1955](#)). The data on which these specifications are based came principally from whole animal studies and those of single cell

systems such as bacteria. In the early stages data from deterministic effects and for stochastic endpoints were not separated. It became clear as time went on that stochastic endpoints had higher RBE values than deterministic endpoints ([Sinclair](#) 1985, [ICRU](#) 1986, [ICRP](#) 1989b, [NCRP](#) 1990).

**Table 6-18. RBE Values (adapted from [NCRP 1954](#))**

Average specific ionization (ion pairs per micron of water)	RBE	Average LET to water (keV per micron)
100 or less <sup>a</sup>	1	3.5 or less
100 to 200	1 to 2	3.5 to 7.0
200 to 650	2 to 5	7.0 to 23
650 to 1500	5 to 10	23 to 53
1500 to 5000	10 to 20	53 to 175

<sup>a</sup>Including x-rays, gamma rays, electrons and positrons.

Alpha particles with LET values of between 53 and 175 keV per micron (which includes the 5.15 MeV alpha particles of <sup>239</sup>Pu) were deemed to have an RBE between 10–20. These values were reiterated in 1963 by the RBE Committee of the ICRP-ICRU (International Commission on Radiation Units and Measurements) ([ICRP-ICRU](#) 1963) and again by the recommendations of the ICRP in 1965 ([ICRP](#) 1965). However, the text of these documents (page 36 of [ICRP](#) [1955] and page 4 of [ICRP](#) [1965]), recommends a value of 10 (as shown in Table 6-19) even though an early statement of the ICRP ([ICRP](#) 1951) had cited an RBE value of 20 for alpha particles compared with radium gamma rays.

**Table 6-19. History of Alpha Particle RBE Recommendations of the ICRP**

Reference	Radiation	Quality factor <sup>a</sup>
<a href="#">ICRP</a> (1951)	Alpha particles compared with radium gamma rays	20
<a href="#">ICRP</a> (1955)	Alpha particles	10
<a href="#">ICRP</a> (1965)	Alpha particles	10
<a href="#">ICRP</a> (1973)	Alpha particles, 2-MeV	20
	5-MeV	15
	10-MeV	10
<a href="#">ICRP</a> (1977)	All alpha particles	20
		Radiation weighting factor ( $w_R$ ) <sup>a</sup>
<a href="#">ICRP</a> (1991)	All alpha particles	20

<sup>a</sup> The terminology for expressing radiation quality has not always been the same, with both RBE and quality factor used in the past and radiation weighting factor introduced recently ([ICRP](#) 1991).

The NCRP, on the other hand, had initially set the alpha particle RBE value at 20 (page 47 in [NCRP \[1954\]](#)) and in 1971 NCRP listed alpha particle RBEs as ranging from 1 to 20 ([NCRP 1971](#)) as shown in Table 6-20. It was about this time that more detailed appreciation of the possible variation of RBE with alpha particle energy was recognized. ICRP Publication 21 ([ICRP 1973](#)) gave alpha particles with an energy of 2 MeV or less an RBE of 20, 5-MeV alpha particles a value of 15, and 10-MeV alpha particles an RBE of 10 (see [Table 6-19](#)).

**Table 6-20. History of Alpha Particle RBE Recommendations of the NCRP**

Reference	Radiation	Quality factor <sup>a</sup>
<a href="#">NCRP (1954)</a>	Alpha particles	20
<a href="#">NCRP (1971)</a>	Alpha particles	1–20
<a href="#">NCRP (1987a)</a>	Alpha particles	20
		Radiation weighting factor ( $w_R$ ) <sup>a</sup>
<a href="#">NCRP (1993a)</a>	Alpha particles	20

<sup>a</sup> The terminology for expressing radiation quality has not always been the same, with both RBE and quality factor used in the past and radiation weighting factor introduced recently ([ICRP 1991](#)).

However, this refinement of different values of RBE as a function of energy was dropped subsequently and 20 became generally used for all alpha particles. It was formalized by the ICRP in Publication 26 ([ICRP 1977](#)) and reiterated in the form of a radiation weighting factor ( $w_R$ ) for alpha particles in the latest ICRP recommendations ([ICRP 1991](#)). The NCRP had also returned to their earlier practice of a single value of 20 for the RBE of alpha particles ([NCRP 1987a](#), [1993a](#)). In the latter reference, the new radiation weighting factor rather than a quality factor was used (see [Section 6.4.4](#)).

Because of their similarity in effects to alpha particles, it is useful also to consider the parallel case of fast neutrons of approximately the average energies observed in fission, i.e., ~1 MeV. The recommended quality factor ( $Q$ ) for these neutrons was 10 from 1954 until 1985. In 1985, the ICRP responded to ICRU Report 40 confirming higher RBE values for neutrons ([ICRU 1986](#)) and changed the  $Q$  value to 20 ([ICRP 1985](#)). The 1986 ICRU values of the maximum RBE at low neutron doses ( $RBE_M$ ) are shown in Table 6-21.

**Table 6-21. Maximum RBE ( $RBE_M$ ) for Fission (or Optimum Energy) Neutrons Compared with Fractionated Gamma Rays ([ICRU 1986](#))**

Endpoint	Range of $RBE_M$
Tumor induction	~3–200
Life shortening	15–45
Transformation	35–70
Cytogenetic studies	40–50
Genetic endpoints in mammalian systems	10–45
Other endpoints	
Lens opacification	25–200
Micronucleus	6–60
Testes weight loss	5–20

In 1987, the NCRP made the same change in the neutron  $Q$  (i.e. from 10 to 20) (NCRP 1987a). The values in a later report of an NCRP committee (NCRP 1990) also confirmed high values for neutron RBEs versus gamma rays (Table 6-22). This is relevant because when fission neutrons and alpha particles have been compared, Sinclair (1985), ratios close to 1 are usually found (Table 6-23). Consequently, we can think of many of the results found with fission neutrons as applying directly to alpha particles. Some comparisons of alpha particles against low-LET radiations are also given in Table 6-23.

**Table 6-22. Summary of Estimated RBE<sub>M</sub> Values for Fission Neutrons Versus Gamma Rays (NCRP 1990)**

Endpoint	Range of RBE <sub>M</sub>
Cytogenetic studies, human lymphocytes in culture	34–53
Transformation	3–80 <sup>a</sup>
Genetic endpoints in mammalian systems	5–70 <sup>b</sup>
Genetic endpoints in plant systems	2–100
Life shortening (mouse)	10–46
Tumor induction	16–59

<sup>a</sup> This value of 80 was derived from a single set of experiments.  
<sup>b</sup> The value of 70 derived from data on specific locus mutations in mice; it is not necessarily an RBE<sub>M</sub>.

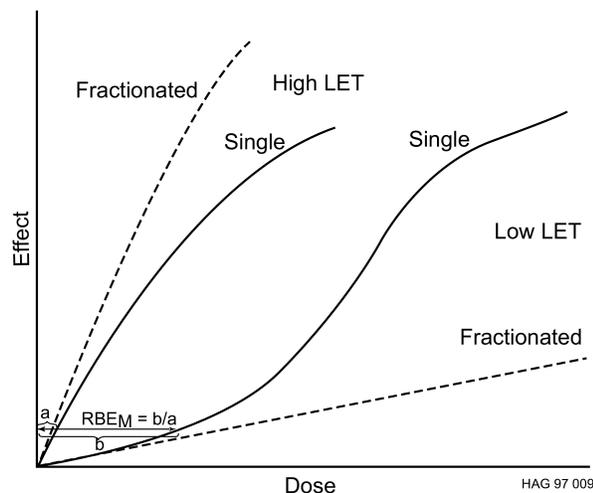
**Table 6-23. RBEs for Alpha Particles Versus Fractionated Low-LET or Neutron Radiations (Sinclair 1985)**

Endpoint	RBE for alpha particles compared to	
	Gamma or beta radiation	Neutron radiation
Chromosome translocations in mouse spermatogonia, <sup>239</sup> Pu (Grahm et al. 1984)		1.0
Chromosome/chromatid fragments in mouse spermatogonia, <sup>239</sup> Pu (Grahm et al. 1984)		1.5
Mutations (HGPRT locus) in human cells <sup>239</sup> Pu (Thacker et al. 1982), estimate	~30	
Chromosome aberrations Edwards et al. 1981		~0.5
Vulpis 1973		~1
Dufraïn et al. 1979		~1
Cancer in dogs, <sup>239</sup> Pu versus <sup>144</sup> Ce-Pr, (Hahn et al. 1984)	~25	
Bone cancer in dogs, <sup>226</sup> Ra versus <sup>90</sup> Sr, (Goldman 1985)	25–50	

### 6.4.3 RBE<sub>M</sub>: The RBE at Very Low Doses

The RBE Committee of the ICRP and the ICRU ([ICRP/ICRU 1963](#)) was the first to point out that the RBE varied with dose because high-LET and low-LET dose response curves have different shapes, Figure 6-4. However, at very low doses the Committee believed that both high-LET and low-LET responses become linear. Thus, the RBE had its maximum value (RBE<sub>M</sub>) and was constant with dose in this low dose region. This is shown in Figure 6-4, which was first published by Sinclair in a review of RBEs in 1983 ([Sinclair 1983](#)) and used also in ICRP Publication 60 ([ICRP 1991](#)). This figure shows the RBE<sub>M</sub> for single exposures and fractionated (or low dose rate) exposures. Fractionated exposures have the same initial slope near zero dose but become less than the acute response for low-LET and more than the acute response for high-LET as shown by the shape of the curve and the way the response varies. In the past, values of RBE were typically established at doses of 0.5 Gy and above. In order to establish an RBE<sub>M</sub>, effects at doses lower than 0.2 Gy must be measured. Fortunately even lower doses of 0.1, 0.05, 0.02 and 0.01 Gy have been used to establish the RBE<sub>M</sub> in more sophisticated systems ([Sinclair 1985](#)).

**The RBE varies with dose because high-LET and low-LET dose response curves have different shapes.**



**Figure 6-4.** Shapes of dose responses for low-LET and high-LET radiations plotted on linear axes ([Sinclair 1983](#)).

In the case of Rocky Flats, we are interested in low dose exposures; therefore, we must establish values of the RBE<sub>M</sub> to use as the basis of the quality factor or for a specific low dose application. In the following discussion it is RBE<sub>M</sub> values that are of interest.

The ICRP and NCRP appear to have settled on 20 as a reasonable value for the RBE<sub>M</sub> of alpha particles of any energy for stochastic endpoints such as carcinogenesis. Differences in RBE between different biological tissues or for plutonium (rather than other alpha emitters) have not been considered in detail by these organizations.

#### 6.4.4 RBE, Quality Factor and Radiation Weighting Factor

Starting in 1954 the term RBE was used for both a measured value of relative effectiveness in an experimental system and for an effectiveness ratio chosen an average of experimental data. The ICRP and NCRP defined this RBE for radiation protection purposes for a particular LET or specific ionization (see [Table 6-18](#)). In 1963 this “legislated value for protection” became known as  $Q$ , the quality factor ([ICRP–ICRU 1963](#)) and various relationships between  $Q$  and LET were developed (see [ICRP 1977](#); [ICRP 1991](#)) ([Figure 6-4](#)). The term RBE was then reserved for actual measured values in particular experimental circumstances, with  $RBE_M$  being identified if the doses were low enough to establish it. In 1991, the ICRP defined equivalent dose (as the average dose in a tissue or organ) in place of dose equivalent (defined at a point). In addition, they proposed single values of  $w_R$ , the radiation weighting factor, for specific incident radiations to express radiation quality. The radiation weighting factor  $w_R$  does not have a specific relationship to LET, but the values were chosen from relevant estimates of  $RBE_M$  expressed in ICRU report 40 ([ICRU 1986](#)) and NCRP report 104 ([NCRP 1990](#)).  $Q$  versus LET relationships can still be used if desired ([ICRP 1991](#)). In 1991 the ICRP recommended a new relationship (see [Figure 6-5](#))<sup>h</sup>. At low LET the relationship is governed by the desire of the ICRP to keep all low-LET radiations ( $<10 \text{ keV } \mu\text{m}^{-1}$ ) the same for radiation protection purposes (see table in ICRP excerpt that follows). The [ICRP \(1991\)](#) wrote as follows:

##### ***Q-L Relationship***

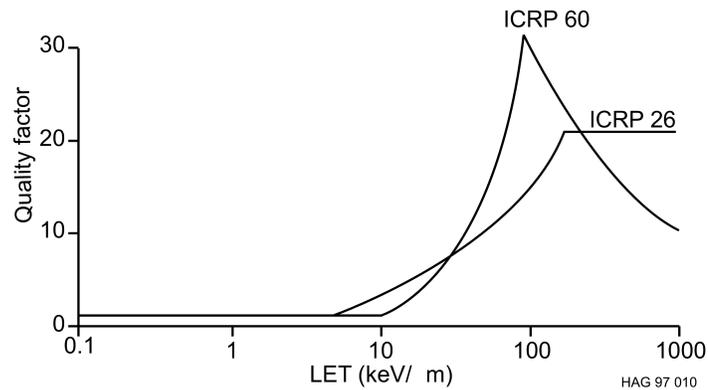
(A8) The Commission has modified its recommendations on the formal relationship between the quality factor,  $Q(L)$ , and unrestricted linear energy transfer,  $L$ , to reflect the higher  $RBE_M$  values for intermediate energy neutrons given in Annex B while maintaining as much simplicity as possible. Simplicity is important to reflect our lack of precise information in man and an appreciation of the practical aspects of radiation protection. For example, the Commission does not believe it is helpful to adopt different quality factor values for different photon energies. The Commission also recognizes the reduced effectiveness of heavy ions with  $L$  greater than  $100 \text{ keV mm}^{-1}$ . The following formulation is adopted.

<b>Specified <i>Q-L</i> relationships</b>	
Unrestricted linear energy transfer, $L$ in water ( $\text{keV } \mu\text{m}^{-1}$ )	$Q(L)^a$
$<10$	1
10-100	$0.32L^{-2.2}$
$>100$	$300 \div \sqrt{L}$

<sup>a</sup>  $L$  expressed in  $\text{keV } \mu\text{m}^{-1}$

This relationship is shown diagrammatically in [Figure 6-5](#).

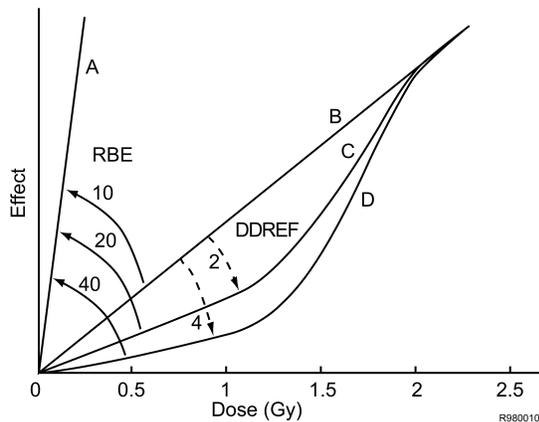
<sup>h</sup> The relationship of  $Q$  versus  $L$  was influenced by the shape of the curve of  $Q$  versus  $y$  (lineal energy, [ICRU 1986](#)) at high values of  $y$ .



**Figure 6-5.** Relationship between quality factor and LET in the recommendations of ICRP Publication 26 (ICRP 1977) and Publication 60 (ICRP 1991).

#### 6.4.5 RBE and DDREF

The DDREF discussed earlier also has uncertainties (Section 6.3.5). However, RBE and DDREF are not independent of one another. For example, in Figure 6-6 if the high LET response is represented by curve A, and the low LET linear response by curve B (the one time standard way of representing low LET data) the RBE is 10, as indeed this value was often quoted in former times. If, however, the low LET response is a linear quadratic with a DDREF of 2 (as in ICRP 1991) curve C, the initial slopes have an RBE of 20, the value most used for alpha particles today.



**Figure 6-6.** Relationship between RBE and DDREF depending on the assumed shape of the dose response.

If the response has a larger DDREF, as would seem to be the case for lung cancer induction, curve D has a DDREF of 4 and an RBE for the initial slopes of 40. In general this pattern is consistent with what we find in practice, for example, we later use an RBE for lung of 30 rather than 20.

This also implies that treating uncertainties in RBE and uncertainties in DDREF independently probably overestimates the uncertainties in the risk coefficients. However, in the absence of an alternative we treat them as if they were independent variables, thus probably overestimating the uncertainties.

#### 6.4.6 Recent Evaluations of Alpha Particle RBEs

The NCRP reviewed experimental data on the RBE of radiations of different quality in Report No. 104 ([NCRP 1990](#)). For alpha particles they considered mainly animal studies with endpoints of bone sarcomas, chromosome aberrations, and lung cancer in which exposure to alpha and beta emitters were compared. The alpha emitters were 15 to 50 times more effective per unit dose, with beta particles probably having about the same effectiveness as gamma rays.

Another general evaluation of alpha particle RBEs for all endpoints is given in a NRPB report ([NRPB 1993](#)) and reproduced here as Table 6-24. The tabulation includes many earlier values of RBE. It does not include a potentially 3 times higher value for lung cancer induction in dogs, namely RBE of 33–58 indicated by [Griffith et al.](#) (1987), quoted on page 149 of NCRP Report No. 104 ([NCRP 1990](#)). Also, the [Brooks](#) (1975) study on chromosome aberrations in the hamster, which gave an estimated RBE of 15 to 20 (page 149 of NCRP Report No. 104), is not included. However, if the two cell mutation entries without ranges are assigned average values 5 and 12, respectively, the average for all the RBE values in the NRPB list is 19.5, with a range from about 5 to 35.

**Table 6-24. Summary of Estimated RBE<sub>M</sub> Values for Alpha Particle Irradiation Compared with Gamma Rays ([NRPB 1993](#))**

Endpoint	RBE	Reference
Bone tumors (dogs)	26	<a href="#">NCRP</a> (1990)
Bone tumors (mice)	25	<a href="#">NCRP</a> (1990)
Bone tumors (dogs)	5.4 (4.0–5.8)	<a href="#">Griffith et al.</a> (1991)
Lung tumors (various species)	30 (6–40)	<a href="#">ICRP</a> (1980)
Lung tumors (dogs)	10–18	<a href="#">Boecker et al.</a> (1988)
Lung tumors (rats)	25	<a href="#">Hahn et al.</a> (1991)
Lung tumors (dogs)	36	<a href="#">Hahn et al.</a> (1991)
Cell transformation (C3H10T½)	10–25	<a href="#">Brenner</a> (1990)
Cell mutation (human lung cells HF19)	Up to 7.1	<a href="#">Cox and Masson</a> (1979)
Cell mutation (Chinese hamster cells. V79)	Up to 18	<a href="#">Thacker et al.</a> (1979)
Chromosome aberrations	5–35	<a href="#">Edwards et al.</a> (1980) <a href="#">Purrott et al.</a> (1980)
Germ cell mutations (chromosome fragments, chromosome translocations, dominant lethals)	22–24	<a href="#">Searle et al.</a> (1976)

[Table 6-24](#) indicates that if RBE values are taken overall without regard to endpoint and without considering plutonium specifically, the central value 20 for the RBE or the radiation weighting factor is quite reasonable. However, the question remains, is this the best we can do for plutonium specifically and for selected endpoints in particular? In the following sections we consider plutonium-induced cancers and chromosome aberrations in lung, liver, bone, and bone marrow. Then, for completeness, we examine new information for some nonstochastic endpoints.

**By treating uncertainties in RBE and DDREF independently we probably overestimate the uncertainties in the risk.**

#### 6.4.7 RBE for Lung Cancer

ICRP Publication 31 ([ICRP 1980](#)) reviewed all animal studies (in mice, rats, and dogs) relating to lung cancer induction both with alpha emitters and beta-gamma emitters. This is the most definitive study of RBEs for lung cancer. In particular, the study noted the difference in the effects of soluble and insoluble alpha emitters. Although the insoluble alpha emitters were somewhat more effective, “hot spot” experiments consistently failed to demonstrate a hot spot effect. The ICRP study concluded that an RBE of 30 with a range from 10–100 best fit all the data for both soluble and insoluble forms of alpha emitters. Values of about 100 were found by [Sanders et al.](#) (1969) for lung tumors in rats. A study documented in [Griffith et al.](#) (1987), cited in NCRP Report No. 104 ([NCRP 1990](#)), yielded values of 30 or more at low dose rates. A recent study in China ([Wu et al.](#) 1992) determined a risk estimate for the induction of lung tumors in rats by plutonium similar to that given by ICRP Publication 31 ([ICRP 1980](#)), which corresponds to an RBE of about 30

Based on these findings, the central estimate for the alpha particle RBE for lung cancer (plutonium included) may be about 30 rather than the generic value of 20 that is used for radiation protection. The uncertainty in this value is of the order of a factor of 3 (i.e., from 10 to 90 or 100). As noted above, the choice depends upon the reference radiation that in this report is based on beta-gamma emitters. The historic combination of reference radiations (beta particles, gamma rays, and x-rays) is now known not to be a self-consistent set ([Section 6.4.1](#)).

#### 6.4.8 RBE for Liver Cancer

There have been numerous studies of the effects of Thorotrast in human beings in different countries in the world, including Germany ([Van Kaick et al. 1984, 1989](#)); Denmark ([Andersson et al. 1994](#)); Portugal ([daMotta et al. 1979](#)); Japan ([Mori and Kato 1991](#)), and the U.S. ([Falk et al. 1979](#)). These studies have been reviewed by UNSCEAR ([UNSCEAR 1994](#)) in the section on thorium. (For further discussion of the Thorotrast studies see [Section 7.3](#)). In these studies, the risk of developing liver cancer is estimated to be about  $300 \times 10^{-4} \text{ Gy}^{-1}$  ([UNSCEAR 1994](#)), although the Danish study ([Andersson et al. 1994](#)) determined risk estimates up to  $700 \times 10^{-4} \text{ Gy}^{-1}$ . Using a  $w_R$  of 20 for alpha particles, a value used by ICRP in specifying risks by site for use in radiation protection ([ICRP 1991](#)), the risk per unit equivalent dose is  $15 \times 10^{-4} \text{ Sv}^{-1}$ . Comparison of these risk estimates with those derived from the LSS is difficult because of the complexities of specifying whether or not liver cancer was the primary cancer. For the LSS data up to 1987, the risk of primary fatal liver tumors is given as  $1.3 \times 10^{-4} \text{ PYSv}^{-1}$  or about  $50 \times 10^{-4} \text{ Sv}^{-1}$  lifetime risk for acute exposure, and  $25 \times 10^{-4} \text{ Sv}^{-1}$  lifetime risk for low dose rate exposure. This agrees reasonably well with  $15 \times 10^{-4} \text{ Sv}^{-1}$  and, thus an RBE of 20 appears

reasonable, but an RBE of 12 would give closer agreement. At the same time, the risk given in the Danish study would suggest an RBE value around 30–45. In the more recent report of the LSS ([Pierce et al. 1996a](#)), two values are given for liver cancer: one for primary liver tumors ( $0.15 \times 10^{-4}$  PYSv<sup>-1</sup> or about  $8 \times 10^{-4}$  Sv<sup>-1</sup> lifetime risk) and the other including liver tumors that are not specified as primary ( $1.14 \times 10^{-4}$  PYSv<sup>-1</sup> or  $55 \times 10^{-4}$  Sv<sup>-1</sup> lifetime). The true risk estimate for primary liver tumors is probably higher than the value specified, that is,  $8 \times 10^{-4}$  Sv<sup>-1</sup>, but lower than the risk estimate of  $55 \times 10^{-4}$  Sv<sup>-1</sup> that includes secondary liver tumors.

Studies of chromosome aberrations in the liver of Chinese hamsters following ingestion of radionuclides, found both <sup>239</sup>Pu and <sup>241</sup>Am were about 15–20 times more effective than either <sup>144</sup>Ce-Pr beta particles or <sup>60</sup>Co gamma rays in inducing chromosome aberrations. Comparison of the effectiveness of <sup>144</sup>Ce-Pr beta particles with <sup>60</sup>Co gamma rays gave a ratio of 1 ([Brooks 1975](#)).

On the basis of these studies, we assign a central value of 20 to the RBE distribution for plutonium for liver tumor induction, with a range from 8 to 50 to describe the 2.5 and 97.5 percentiles of the distribution, respectively.

#### 6.4.9 RBE for Bone Sarcomas

It is evident from data presented in Table 7.3 of NCRP Report No. 104 ([NCRP 1990](#)) that in terms of average skeletal dose, bone sarcoma induction by <sup>226</sup>Ra may, at the lowest doses, be ~25 times more effective than <sup>90</sup>Sr for both dogs and mice. These values may be somewhat exaggerated by using extreme values for the initial slope of the response curves for <sup>90</sup>Sr. The average RBE for <sup>226</sup>Ra is 20 for the two lowest dose groups of beagles and mice. Both radium and strontium are chemically similar to calcium and tend to be similarly distributed throughout the bone volume. The sensitive cells for induction of bone cancer are believed to be in the endosteal layer on bone surfaces i.e. endosteal cells. If this is true, the comparison on the basis of average skeletal dose is reasonable for these two nuclides because they are both uniformly distributed in bone.

Plutonium-239 appears to be 15–17 times more effective than <sup>226</sup>Ra in inducing bone cancer (Table 6.4 of [NCRP 1990](#)). However, it is well known that <sup>239</sup>Pu deposits preferentially on bone surfaces and delivers more dose to the nearby target cells. Doses are routinely calculated for bone surface cells for bone-seeking radionuclides ([ICRP 1989a](#)). It has been estimated that the dose to endosteal cells is 7.5–9 times greater for <sup>239</sup>Pu than for <sup>226</sup>Ra ([Marshall et al. 1978](#); [Puskin et al. 1992](#)). Thus, in terms of the dose delivered to the critical cells, <sup>239</sup>Pu is about twice as effective as <sup>226</sup>Ra in producing bone cancer. Using the results from [NCRP \(1990\)](#), the RBE for <sup>239</sup>Pu for bone cancer production compared to <sup>90</sup>Sr is estimated to be 40–50.

[Lloyd et al. \(1995\)](#) presents estimates of toxicity of <sup>239</sup>Pu and other alpha emitters relative to <sup>226</sup>Ra. The comparisons are based on average skeletal dose. For a single exposure to monomeric plutonium, a toxicity ratio of  $16 \pm 5$  was estimated; for protracted exposure due to migration from an extraskeletal deposit, a toxicity ratio of  $32 \pm 10$  was estimated. When adjusted for dose to the sensitive cells, these ratios would be 8 for the single exposure and 16 for the protracted exposure. For <sup>224</sup>Ra which is another nuclide that delivers most of the dose to endosteal cells, toxicity ratios of  $6 \pm 2$  for a single exposure and  $16 \pm 5$  for chronic exposure were estimated. These values are consistent with those for plutonium. [Lloyd et al. \(1995\)](#) also compared <sup>90</sup>Sr to <sup>226</sup>Ra. At low doses, the relative toxicity of <sup>226</sup>Ra to <sup>90</sup>Sr was  $20 \pm 12$ ; at very low doses, few

cancers were observed from  $^{90}\text{Sr}$  exposure so that the estimate of relative toxicity is large but highly uncertain. Using the [Lloyd et al. \(1995\)](#) data to estimate the toxicity of  $^{239}\text{Pu}$  relative to  $^{90}\text{Sr}$  at low doses, a range of 160–320 is found. On the basis of these studies the uncertainty distribution for the plutonium RBE for bone tumor induction probably has a 50th percentile value of about 50 with the 2.5 and 97.5 percentiles ranging from about 15 to 320, respectively.

Another estimate of bone tumor risk for alpha particles derives from studies with Thorotrast. [Hunacek and Kathren \(1995\)](#) reviewed the German, Japanese and Portuguese studies determined a risk estimate for alpha particles in bone of  $0.002 \text{ Gy}^{-1}$ , with a range from  $0.0016 \text{ Gy}^{-1}$  to  $0.120 \text{ Gy}^{-1}$ . The value preferred by the authors is at the very low end of the range given, which encompasses the earlier ranges  $0.055 \text{ Gy}^{-1}$  to  $0.120 \text{ Gy}^{-1}$  given by [Mays and Spiess \(1979\)](#) and BEIR IV ([NAS/NRC 1988](#)) (see also [Table 7-2](#), of this report). To derive an RBE from these risk estimates requires a measure of the risk of fatal bone cancer from low-LET radiation. An approximate estimate of the lifetime risk of fatal bone cancer was made earlier ([Section 6.2](#) and [Table 6-4](#)) and has the value  $0.032 \times 10^{-2} \text{ Sv}^{-1}$ . Using this value, the RBE value could range from about 5–375, somewhat larger than the range derived from the studies with  $^{224}\text{Ra}$  and  $^{239}\text{Pu}$ .

The choice of a suitable distribution that is consistent with all the above information on RBEs is not simple. After considering a number of possibilities for lognormal distributions we selected one with a 50th percentile at 50, and a GSD of 2.8. The 2.5 and 97.5 percentiles of this distribution were 6.7 and 375, respectively. However, the upper tail of the distribution was truncated at 400 to remove the low probability of sampling what we consider unrealistically large RBE values.

#### 6.4.10 RBE for Leukemia

An estimate of the RBE for leukemia can be derived from the induction of myeloid leukemia in the Thorotrast series. This has also been noted by [Boice \(1993\)](#). Leukemia is induced less frequently than liver tumors but the dose to the bone marrow is also less than that to the liver. [UNSCEAR \(1994\)](#) derived a leukemia risk estimate of about  $50 \times 10^{-4} \text{ Gy}^{-1}$  which is almost the same as the risk estimate for exposure to low-LET radiation (i.e., this result is more consistent with an RBE of  $\sim 1$ ) ([Boice 1993](#)). However, a more recent reevaluation of the German, Japanese, and Portuguese Thorotrast studies, including the dosimetry, lead to a higher risk estimate for leukemia of about  $320 \times 10^{-4} \text{ Gy}^{-1}$  ([Hunacek and Kathren 1995](#)). The corresponding RBE would be 6–7 (see [Section 7.4](#)).

Relatively low RBE values for leukemia are supported rather strongly by studies of myeloid leukemia in animals using fission neutrons, in which RBE values of the order of 2–3 are obtained rather than the usually high RBE values associated with other endpoints ([Ullrich and Preston 1987](#)). Another study in young mice ([Maisin et al. 1996](#)) found an RBE “of the order of 1 and certainly below 3” for 3.1 MeV neutrons versus x-rays. Although these studies are with thorium (alpha energy, 4.0 MeV) and not plutonium (alpha energy, 5.1 MeV), studies with a range of alpha particle energies have not shown a great difference in effectiveness ([Miller et al. 1996](#); [Howell et al. 1994](#)). Thus, for bone marrow (i.e., leukemia induction) it appears reasonable to consider a low value for the alpha particle RBE. For our analysis we selected a 50th percentile value of 3 for the RBE for leukemia with a range from 1 to 10 to represent the 2.5 and 97.5 percentiles of the distribution, respectively.

### 6.4.11 RBE for Whole Body

An RBE for whole body is rarely meaningful in the case of alpha-emitting radionuclides because rather than being uniformly distributed in body tissues, most alpha emitters tend to localize preferentially in specific tissues or organs. For a hypothetical alpha emitter distributed uniformly throughout all body tissues, an average value of RBE for whole-body exposure is conceptually possible. Furthermore, such an average RBE could be derived by analogy with fast neutron experience because, as shown in [Table 6-23](#), where comparisons are possible, alpha particles and fission neutrons have very similar RBEs.

In the case of neutrons, the small animal bodies (mice) used experimentally are irradiated more or less uniformly. Furthermore, lifeshortening at lower doses has been shown to be entirely the result of tumorigenesis ([UNSCEAR 1982](#)) i.e. no non-specific cause of aging due to radiation has been found. RBEs for fission neutrons for lifeshortening in mice have been extensively investigated at Oak Ridge National Laboratory ([Storer and Ullrich 1983](#)) and at Argonne National Laboratory (Thomson et al. [1981a](#), [1981b](#)). These have been reviewed by Sinclair ([Sinclair 1985](#)), by ICRU-ICRP ([ICRU 1986](#)), and by NCRP ([NCRP 1990](#)). In brief, the RBEs of neutrons compared to gamma rays for single exposure are in the range from 10–16, for fractionated exposure the range is 15–20, and the range is up to 40–50 for continuous exposure ([NCRP 1990](#)). Thus, the whole-body exposure RBEs in a similar range to those chosen above for liver (central value of 20 with range from 8–50), apply to fission neutron exposure and presumably to alpha emitter exposure if the alpha emitter were uniformly distributed throughout all body tissues. However, for plutonium, which localizes in lung, liver, and bone, this conceptual RBE does not apply. Consequently, an entry for whole-body RBE is not included in [Table 6-25](#).

### 6.4.12 Other Endpoints

The following discussion of relatively new findings for other endpoints is included for completeness. These endpoints are not directly related to the issue of cancer risk assessment following inhalation of environmental concentrations of plutonium, but they are relevant to a general consideration of alpha particle RBEs.

**6.4.12.1 RBEs for Alpha Particles for Deterministic Effects.** Typically, alpha particle RBEs for deterministic effects are lower than for stochastic effects (just as with fission neutrons) and are often on the order of 5 or 6 ([ICRP 1989b](#)). Using testicular spermhead survival in the mouse as the endpoint, [Howell et al.](#) (1994) showed that the RBE ranged from 8 for 4-MeV alpha particles to 4 for 10-MeV alpha particles. That is, the RBE depended upon alpha-particle energy, and the peak response was at an LET of 90 keV m<sup>-1</sup> or higher. This work has been extended further in a recent report ([Howell et al.](#) 1997).

Unusually high values of alpha particle RBEs were found recently for another deterministic effect, namely developing hematopoiesis in mice ([Jiang et al.](#) 1994). Alpha-particle RBEs were of the order of 250–360 when compared with continuous gamma ray exposure and 130–180 if the reference point was the effect of acute gamma ray doses. Such high values are quite unusual.

**6.4.12.2 Effects Unique to Alpha Particles.** There have also been suggestions from time to time that alpha particles have unique effects not seen with low-LET radiation and, thus, effectively have an infinite RBE. One such example concerned genetic transmissibility of

damage in which clonal defects induced by alpha particles turn up many clonal generations later (Khadim et al. 1992). However, the search for x-ray effects of the same type was not exhaustive; thus, they could have been present in low frequency. Indeed, an early paper (Sinclair 1964) and a recent paper on genomic instability found these effects with x-rays as well as with alpha particles (Manti et al. 1997) and even more recently with neutrons and gamma rays (Ponnaiya et al. 1997). Thus these effects are not unique to alpha particles.

#### 6.4.13 Summary of RBE Values and Uncertainties

While an RBE value of 20 for alpha particles for general use in radiation protection may be adequate, it may not be the most appropriate for specifying the RBE in selected organs for risk estimation. Table 6-25 summarizes the central estimates (50th percentile) of RBE and the preferred uncertainty bounds (2.5 – 97.5 percentiles) used in the present analysis. The RBE for lung is estimated to have a 50th percentile value of 30 rather than 20 with a range from 10 (2.5 percentile) to 100 (97.5 percentile). The RBE for liver has somewhat lower values; a 50th percentile of 20 is chosen with a range from 8 (2.5 percentile) to 50 (97.5 percentile). For the induction of bone tumors, the RBE value is critically dependent on the dose basis used. Plutonium is more effective than  $^{226}\text{Ra}$  but similar to  $^{224}\text{Ra}$ . If the dose is specified to the endosteal cells,  $^{239}\text{Pu}$  has an RBE of the order of 50 with a range from 5–375. For purposes of the Rocky Flats analyses, the RBE is represented by a distribution in which the 50th percentile is 50, with 2.5 and 97.5 percentiles of 6.7 and 375, respectively. The maximum is truncated at 400 to remove the small possibility of sampling what we consider unrealistically large RBE values. For the induction of leukemia, the value is much lower (an RBE of 3), with a range from 1 (2.5 percentile) to 10 (97.5 percentile). Note that the result giving the lowest RBE was not obtained from studies with plutonium.

**Table 6-25. RBE Uncertainties for Cancer Induction by Plutonium,  $f(B_i)$**

Organ or tissue	Preferred percentiles 50 (2.5, 97.5)	Selected distribution and parameters GM; GSD	Resulting percentiles 50 (2.5, 97.5)
Lung	30 (10, 100)	lognormal GM = 30; GSD = 1.81	30 (9, 96)
Liver	20 (8, 50)	lognormal GM = 20; GSD = 1.60	20 (8, 50)
Bone	50 (5, 375)	lognormal GM = 50; GSD = 2.80	50 (6.7, 375) <sup>a</sup>
Bone marrow	3 (1, 10)	lognormal GM = 3; GSD = 1.80	3 (0.95, 9.5)

<sup>a</sup> Distribution truncated at 400.

### 6.5 Calculation of Lifetime Risk Coefficients of Cancer Mortality and Uncertainties Following Exposure of a U.S. Population to High-LET Radiation

Lifetime risk coefficients of cancer mortality for exposure to high-LET radiation ( $*R_{USi}$ ) are calculated for a U.S. population using the distribution of low-LET lifetime risk coefficients determined in [Section 6.3.6](#) and presented in [Table 6-16](#), multiplied by the appropriate distribution for the RBE factor presented in [Table 6-25](#). The two sets of values are reproduced in [Table 6-26](#). We perform the calculation using a Monte Carlo random sampling technique, according to the following equation.

$$*R_{USi} = f(R_{USi}) \times f(B_i) \quad (6-2)$$

where:

$f(R_{USi})$  = distribution function for the lifetime risk coefficient for low-LET radiation (% per Gy), calculated using Equation (6-1)

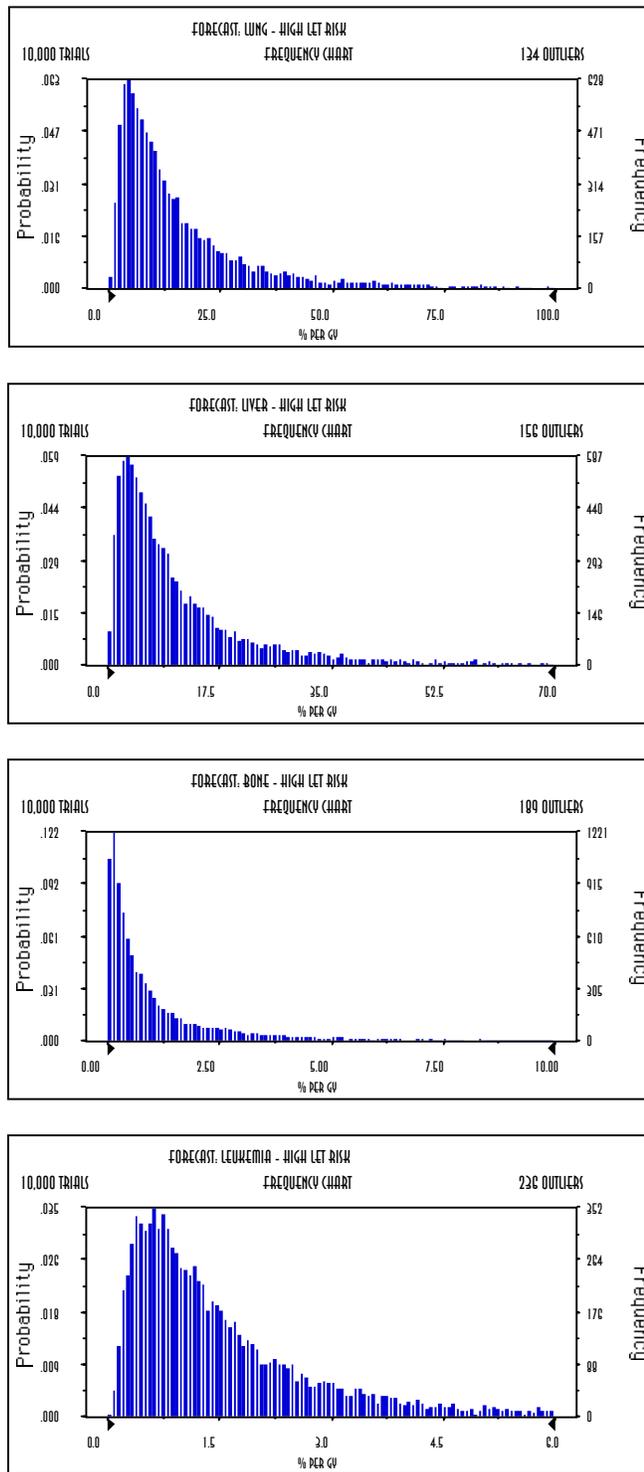
$f(B_i)$  = distribution function for the RBE for alpha radiation from plutonium (unitless).

For each cancer site a total of 10,000 iterations were made using the Monte Carlo sampling technique to establish the distribution of  $*R_{USi}$ . It was assumed that there is no correlation between any of the parameters included in the uncertainty analysis. The output distributions are summarized in [Table 6-26](#) and illustrated in [Figure 6-5](#). In all cases, the resulting output distribution is positively skewed so that the mean value is larger than the median value. The distributions are approximately lognormal. The high-LET risk coefficients have larger coefficients of variation compared to the low-LET risk coefficients. The risks of high-LET radiation follow those for low-LET, as modified by the estimated RBE distribution for each of the cancer sites considered ([Table 6-25](#)). The leukemia, liver, and lung median risk coefficients vary by about a factor of 5 to 7 in either direction. Again, the uncertainty in the bone risk coefficient is the largest and varies by more than an order of magnitude in either direction from the median estimate.

**Table 6-26. Lifetime Fatal Cancer Risk Coefficients ( $10^{-2} \text{ Gy}^{-1}$ ) for a U.S. Population Exposed to High-LET Radiation Determined From the LSS Low-LET Risk Coefficient Combined with an RBE for Alpha Radiation**

Cancer site	RBE			Lifetime fatal cancer risk coefficient					
				Low-LET			High-LET <sup>a</sup>		
	Percentiles			Percentiles			Percentiles		
2.5	50	97.5	2.5	50	97.5	2.5	50	97.5	
Lung	9	30	96	0.10	0.37	2.0	1.9	11.0	76
Liver	8	20	50	0.076	0.39	2.1	1.1	7.7	58
Bone	7	50	375	0.002	0.012	0.094	0.04	0.6	8.6
Bone marrow (leukemia)	1	3	10	0.13	0.40	1.1	0.2	1.2	5.9

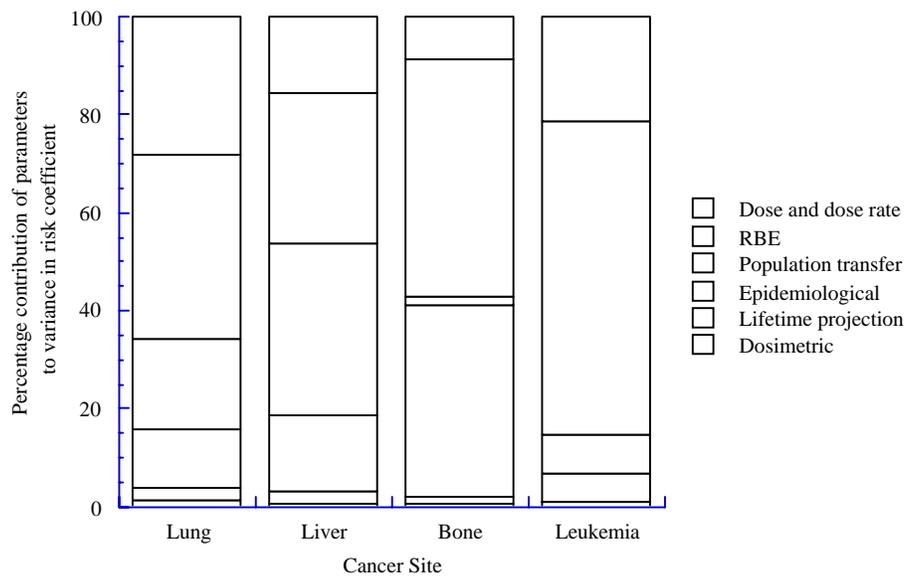
<sup>a</sup> Calculated from the two preceding distributions according to [Equation 6-2](#).



**Figure 6-7.** Uncertainty distributions for the lifetime risk coefficients of cancer mortality for exposure to high-LET radiation for lung, liver, bone, and bone marrow.

### 6.5.1 Sensitivity Analysis

We have conducted a sensitivity analysis to determine which factors contribute the most to the uncertainty in the final estimates of lifetime risk from exposure to high-LET radiation for each cancer site. [Figure 6-6](#) summarizes these values. These results show that uncertainty in the RBE is a major source of uncertainty for all the cancer sites considered. The RBE is the dominant source of uncertainty in the leukemia high-LET risk estimate, where the increased risk of cancer because of radiation exposure is well established. The effect of dose and dose rate (DDREF) is the next most important factor. However, their importance may be exaggerated because RBE and DDREF are treated as independent parameters (see [Section 6.4.5](#)). There are significant differences between the different cancer sites studied here. For bone, uncertainty in the RBE is the dominant source of uncertainty, but epidemiologic uncertainties (98% of which are statistical uncertainties), are also large (39%). Epidemiologic uncertainties, again mostly statistical uncertainties, account for 12–16% of the uncertainty for the lung and liver cancer risk coefficients. Uncertainty in the method of transferring the risk from the Japanese population to a U.S. population accounts for 35% of the uncertainty in the liver risk coefficients and 19% of the uncertainty in the lung risk coefficients.



**Figure 6-8.** Sensitivity analysis for high-LET lifetime risk coefficients.

## 7. RISK ESTIMATES BASED UPON STUDIES OF HUMANS EXPOSED TO OTHER ALPHA-EMITTERS

Human experience with other alpha-emitting radionuclides can be used to obtain estimates of the risks to people exposed to plutonium. Alpha-emitting radionuclides that deposit in tissues of primary concern (lung, liver, bone and to a lesser extent bone marrow; see [Chapter 2](#)) are of greatest interest. Although the tissue distributions are not necessarily exactly the same as for plutonium, the risk coefficients (risk per unit absorbed dose) for particular tissues should be broadly comparable. The doses are due to absorption of alpha particles having energies between 4 and 9 MeV. Differences in the RBE of these radiations and the alpha particles of  $^{239,240}\text{Pu}$ , which have energies of about 5.2 MeV are minor. Human experience with other alpha-emitters and interpretations of those findings are discussed in sections that follow.

For inhalation exposures, the lung is the primary tissue at risk. [Section 7.1](#) considers estimates of risk from other alpha-emitters in the lung. [Section 7.2](#) discusses risk estimates for cancer of the liver, and [Section 7.3](#) provides estimates of risk for bone cancer. [Section 7.4](#) discusses data available to estimate leukemia risks as a result of irradiation of the bone marrow. [Section 7.5](#) summarizes the risk estimates derived from human exposures to other alpha-emitters.

**Although there are differences in dose distribution in the exposed tissues, risk coefficients for plutonium should be broadly comparable to those for other alpha-emitters deposited in lung, liver, and bone.**

Radiobiological studies have identified specific tissues and categories of cells whose irradiation is believed to be responsible for the incidence of certain cancers. Radiation dose estimates often focus on those tissues or cell groups, rather than averaging over a whole organ or region as was often done in the past. The basal and secretory cells of the bronchial and alveolar epithelium in the lung may be most important for the development of lung cancer. Dose estimates for the bronchial epithelium are used as a primary measure of exposures to radon progeny. No critical tissue or cell type has been identified for induction of liver cancer; consequently, doses are still averaged over the entire organ. For bone cancer, the cells lining the endosteal surfaces appear to be most important. Irradiation of the bone marrow is considered the causative factor in radiation-induced leukemia. Doses to bone marrow are explicitly evaluated when assessing leukemia risks.

### 7.1 Risk Estimates for Lung

Most of our knowledge of the risks of lung cancer from exposure to alpha radiation has been derived from studies of persons exposed to radon and its decay products (also called radon progeny; see [Glossary](#)). Although there are clearly differences in deposition and dose distribution between plutonium and radon decay products, the absence of other information regarding radiogenic lung cancer in humans leads one to examine studies of exposure to radon decay products. First, [Section 7.1.1](#) discusses radon dosimetry, which is frequently estimated in terms of unusual historic units. Estimates of lung cancer risk in miners exposed to radon decay products are reviewed in [Section 7.1.2](#). [Section 7.1.3](#) describes our application of the most recent radon cancer risk estimates to plutonium exposures. [Section 7.1.4](#) summarizes the risk estimates for plutonium and the associated uncertainties.

### 7.1.1 Dose Estimates for Radon Exposures

The historic unit of radon exposure, the working level month (WLM), represents a cumulative exposure to a concentration of one working level (WL) for one working month, taken to be 170 hours. The concentration of one WL refers to any combination of short-lived radon progeny in a liter of air that will result in the emission of  $1.3 \times 10^5$  MeV of potential alpha particle energy. Although we refer to “radon exposure” it is the decay products that cause most of the dose that people receive. The short-lived alpha-emitting radionuclides of interest are those that follow decay of radon-222 ( $^{222}\text{Rn}$ ); namely, polonium-218 ( $^{218}\text{Po}$ , also called radium A or RaA), lead-214 ( $^{214}\text{Pb}$ , RaB), bismuth-214 ( $^{214}\text{Bi}$ , RaC) and polonium-214 ( $^{214}\text{Po}$ , RaC'). This sequential decay is illustrated in the [Glossary](#).

Conversion from working level months to physical dosimetry units depends on several factors. For a mining environment, it has been estimated that an exposure of 1 WLM leads to an absorbed dose to the sensitive cells of the bronchial epithelium of 5 mGy (0.5 rad) ([NCRP 1984](#); [NAS/NRC 1991](#)). For exposure to radon in less dusty environments than mines, the conversion to

**The BEIR VI report concluded there was little difference in the median values of dose per unit exposure at home or in mines. Differences between men and women were small and age had little effect on this parameter.**

dose was believed to be different. NCRP Report No. 78 ([NCRP 1984](#)) gave estimates of 7 mGy  $\text{WLM}^{-1}$  (0.7 rad  $\text{WLM}^{-1}$ ) for men and 6 mGy  $\text{WLM}^{-1}$  (0.6 rad  $\text{WLM}^{-1}$ ) for women for environmental exposures. The companion report to BEIR IV ([NAS/NRC 1991](#)) estimated that exposure at home to a WLM results in an absorbed dose of 7 mGy (0.7 rad) to the bronchial epithelium for both sexes.

In the assessment of exposure from natural background radiation, NCRP Report No. 94 ([NCRP 1987b](#)) estimated that dose conversion factors were 5 and 6 mGy  $\text{WLM}^{-1}$  (0.5 and 0.6 rad  $\text{WLM}^{-1}$ ) to the bronchial epithelium for lifetime exposure of males and females, respectively. In that report, the estimate for uranium miners was 3 mGy  $\text{WLM}^{-1}$  (0.3 rad  $\text{WLM}^{-1}$ ). This difference was attributed in part to differences in the assumed aerosol characteristics for miners and the indoor environment, and in part to decreased deposition at the higher air flows required for the higher breathing rates of working miners.

In ICRP Publication 50 ([ICRP 1987](#)), the mean dose conversion coefficients for reference conditions are 4.7 mGy  $\text{WLM}^{-1}$  (0.47 rad  $\text{WLM}^{-1}$ ) for the bronchial epithelium and 0.65 mGy  $\text{WLM}^{-1}$  (0.065 rad  $\text{WLM}^{-1}$ ) for the pulmonary tissue. The latest ICRP report on radon ([ICRP 1993b](#)) does not provide a dosimetric evaluation, but it does compare detriment from radon exposure to that from other radiation exposure. The result is not comparable to the other dose estimates given here.

The BEIR VI committee has performed a detailed review of the dosimetric factors for the two types of exposure ([NAS/NRC 1998](#)). Exposures in homes with and without smokers present were considered. They concluded that there is little difference in median values of dose per unit exposure at home or in mines. They also found no differences between the median dosimetric factors for males and females or between those for adults and children aged 10 years. Small differences (maximum of 8%) between median values for adults and older children and those for infants were found. The BEIR VI report gives an estimate of the dose conversion factor for miners that is based upon the new ICRP lung model. That result is 7.0 nGy  $\text{h}^{-1}$  per  $\text{Bq m}^{-3}$  of radon. For equilibrium conditions, this corresponds to 4.3 mGy  $\text{WLM}^{-1}$  (0.43 rad  $\text{WLM}^{-1}$ ).

[Nero et al.](#) (1986) estimated that average concentrations of radon progeny in homes in the U.S. were about 0.007 WL. Continuous exposure at this level would result in an annual exposure of 0.36 WLM ( $0.007 \text{ WL} \times 8760 \text{ h y}^{-1} \div 170 \text{ h M}^{-1} = 0.36 \text{ WLM y}^{-1}$ ) to members of the public at home continuously. The more recent National Radon Survey found a geometric mean concentration of radon in dwellings of 0.67 pCi L<sup>-1</sup> with a geometric standard deviation of 3.1 ([Marcinowski et al.](#) 1994). The corresponding average concentration is about 1.3 pCi L<sup>-1</sup>, which (for an equilibrium ratio of 0.4 and an occupancy fraction of 0.7) results in an annual exposure of about 0.2 WLM. Average doses to U.S. residents can be estimated using the BEIR VI dosimetry estimate of 4.3 mGy WLM<sup>-1</sup> (0.43 rad WLM<sup>-1</sup>) and the finding that differences in the dose factors between mines and homes ([NAS/NRC](#) 1998) are small. The estimated dose to the bronchial epithelium is 0.9 mGy y<sup>-1</sup> (0.09 rad y<sup>-1</sup>) from exposure to the mean radon concentration in U.S. homes reported by [Marcinowski et al.](#) (1994). This estimate applies to men, women, and children exposed under the conditions assumed.

### 7.1.2 Review of Risk Estimates Based upon Exposure to Radon

There have been a number of estimates of the risk of lung cancer from human exposure to radon and its decay products, which emit energetic alpha particles. [Table 7-1](#), which summarizes those estimates, is an updated version of the summary table in NCRP Report No. 115 ([NCRP](#) 1993b). The estimates of excess absolute risk, arranged in chronological order, provide some perspective on the uncertainty in radon lung cancer risk coefficient and the different approaches used to estimate it. All these estimates refer to the traditional unit of cumulative exposure to radon progeny, the working level month described in [Section 7.1.1](#).

Differences in the radon-induced lung cancer risk estimates are due to differing assumptions about modeling, smoking, and other factors. For example, the range of values from [ICRP](#) (1987) reflects the difference between relative and absolute risk projections for their European reference population, for which lifespans and lung cancer incidence rates for males and females were specified. The second estimate in that row is the result of applying the model used in ICRP Publication 50 ([ICRP](#) 1987) to the 1980 U.S. population ([NCRP](#) 1993b). This value is in good agreement with the BEIR IV estimate, derived using a relative risk model for an exposure of 0.1 WLM y<sup>-1</sup>, for the same population. As the comparison above shows, calculations of risks for a particular population depend upon the lung cancer risks for smokers and non-smokers and the prevalence of smoking in the population. The baseline lung cancer risk for the U.S. or other reference populations has varied with time, reflecting changes in smoking habits. Baseline lung cancer risks for Colorado are discussed in [Section 7.1.3](#).

The uncertainty analysis of [Puskin](#) (1992) addressed many aspects of the radon risk question but did not quantify the effect of smoking. The most recent ICRP ([ICRP](#) 1993b) estimate is quite close to Puskin's central value and was rounded to one significant figure.

Also shown in the table are results of a recent and more extensive analysis of the miner data by [Lubin et al.](#) (1994) and in slightly revised form by [Lubin et al.](#) (1995). Their final model, based on pooled data from 11 studies of cohorts of underground miners, considers time since exposure, attained age, and exposure level. The exposure level is important for examining the "inverse dose rate" effect. That is, there are fewer lung cancers produced per unit dose at high dose rates than are found at lower dose rates. This is the opposite of the dose rate effect found for

**Table 7-1. Estimates of Lifetime Lung Cancer Mortality Risks from Lifetime Exposure to Radon Decay Products Based on Studies in Miners**

Source of estimate	Excess lifetime lung cancer mortality (deaths per 10 <sup>6</sup> P-WLM) <sup>a</sup>
<a href="#">UNSCEAR</a> (1977)	200–450
<a href="#">NAS/NRC</a> (1980), BEIR III	730
<a href="#">NCRP</a> (1984)	130
<a href="#">ICRP</a> (1987)	170–230 <sup>b</sup> , 360 <sup>c</sup>
<a href="#">UNSCEAR</a> (1988)	150–450
<a href="#">Puskin and Yang</a> (1988)	(115–400)
<a href="#">NAS/NRC</a> (1988), BEIR IV	350
<a href="#">Puskin</a> (1992)	140–570 <sup>d</sup>
<a href="#">ICRP</a> (1993b)	300
<a href="#">Lubin et al.</a> (1995)	200 <sup>e</sup>

<sup>a</sup> P-WLM = person-working level months; the WLM is the traditional measure of exposure to radon decay products (see [Section 7.1.1](#)).

<sup>b</sup> For models applied to the reference population defined in [ICRP](#) Publication 50 (1987).

<sup>c</sup> For the 1980 U.S. population, used in BEIR IV report ([NAS/NRC](#) 1988).

<sup>d</sup> The central (geometric mean) estimate was 283; bounds reflect an estimated 90% confidence interval, derived without considering the uncertainty due to smoking.

<sup>e</sup> For the estimated average concentration to which miners were exposed.

low-LET radiation exposure (see [Section 6.3.5](#)). The inverse dose rate effect has been observed in studies of miner populations exposed to radon progeny. [Lubin et al.](#) (1994) found, from comparisons among the higher dose groups, that there was a consistent enhancement of risk associated with protracted exposure. This phenomenon was termed “protraction enhancement.” Further analysis has shown that the protraction enhancement effect is less at lower exposures to radon progeny. For exposures lower than about 50 WLM, [Lubin et al.](#) (1995) conclude that there may not be a protraction enhancement effect. For that reason, they suggested that their model may overestimate risk at low exposures.

**Below a cumulative exposure of ~50 WLM, which corresponds to a dose of ~0.2 Gy (~20 rad) to the bronchial epithelium, there may be no enhancement of risk due to protraction of exposure.**

For a radon progeny concentration of 2.8 WL, the average concentration of radon in the 11 miner studies, the preferred model of [Lubin et al.](#) (1995) gives a risk estimate for miner exposures of 200 excess deaths per 10<sup>6</sup> persons per WLM. This is 56% of the BEIR IV value. For radon progeny concentrations less than 0.1 WL, the preferred model yields a risk estimate that is about 1.5 times that of the BEIR IV value ([NAS/NRC](#) 1988). This comparison illustrates the inverse dependence of the risk upon concentration using the preferred model of [Lubin et al.](#) (1995).

The BEIR VI report ([NAS/NRC](#) 1998) reexamines many facets of the problem of radon exposure and the risks to the general population. After considering four alternative approaches, the BEIR VI committee chose to follow the general empirical approach of the BEIR IV committee and to base risk estimates upon empirically derived models. It chose a relative risk model based upon the work of [Lubin et al.](#) (1994) and extends that work.

The BEIR VI report is notable in several respects. First, it provides updated results for the 11 miner studies previously analyzed by Lubin et al. (1994, 1995). Second, the very recent meta-analysis of case-control studies of residential radon and population exposures (Lubin and Boice, 1997) has been compared with miner studies. Dosimetric factors were also reevaluated (see Section 7.1.1) and estimates of risk are presented for smokers and nonsmokers as well as for the general population. Results of a detailed uncertainty analysis are also provided in an appendix to the report.

Data from the studies of miners were reanalyzed using two preferred models, the exposure-age-duration (E-A-D) model and the exposure-age-concentration (E-A-C) model. Both consider effects of time since exposure and the attained ages of the miners. The first model also includes duration of exposure while the second model explicitly considers the radon progeny concentration level. The relative risk of lung cancer was found to decrease as time since exposure and as attained age increased. In the first model, the relative risk increases for longer periods of exposure. In the E-A-C model, exposures at concentrations above 0.5 WL are estimated to produce lower relative risks and the concentration modifying factor is less than 1. Home exposures to radon are at much lower levels and the concentration modifying factor is equal to its maximum value of 1.

The BEIR VI report contains estimates of lifetime relative risks of indoor exposure to radon for smokers and nonsmokers for both models. The committee examined the question of the interaction between smoking and radon. Evidence of synergism between the two carcinogens was found. The combined effects of smoking and exposure to radon were greater than would be expected if the effects were additive but less than those expected if the risks were multiplicative. Although the interaction could not be characterized with confidence, the committee believed that a submultiplicative model best represents the available data. Estimates of lifetime relative risks of radon exposure are presented for both the preferred model and for a multiplicative model (NAS/NRC 1998).

The lifetime relative risks of radon exposure that are estimated in the BEIR VI report depend upon the model selected. The E-A-C model yields higher risks than the E-A-D model. Table 7-2 contains averages of estimates of excess lifetime relative risk for the cumulative indoor exposure range of interest (<50 WLM). The averages are based on four estimates (for cumulative exposures of 6.8, 14, 27, and 41 WLM in 70 years) made using the sub-multiplicative model of the interaction between smoking and radon. There is little variation (<10%) in the estimated risks over this exposure range.

The lifetime risk estimates derived using the E-A-C model for the population groups in Table 7-2 are about 33% larger than those from the E-A-D model. The E-A-C model is taken as the reference point for these comparisons; for example,  $(0.013 - 0.0086)/0.013 = 0.34$ . This difference is smaller than the uncertainty on the underlying risk estimate derived from the miner studies. For the exposure-age-concentration model, the geometric mean and geometric standard deviation for  $\beta_R$ , the excess relative risk coefficient for exposure to radon, were estimated to be  $0.077 \text{ WLM}^{-1}$  and 1.36, respectively. This gives a 95% confidence interval of 0.042–0.14  $\text{WLM}^{-1}$ ; the ratio of the two bounds is about 3.4. This range also encompasses results from BEIR IV, which are 60–80% lower than those estimated using the E-A-C model of BEIR VI. For the same assumptions used in deriving the BEIR IV risk estimate shown in Table 7-1, a comparable estimate for the BEIR VI models would be 400–600 lung cancer deaths per  $10^6$  P-WLM.

**Table 7-2. Estimates of Excess Relative Risk of Lung Cancer Due to Lifetime Exposure to Low Concentrations of Radon (NAS/NRC 1998)**

Exposed group	Excess lifetime relative risk per WLM <sup>a</sup>	
	Exposure-age-concentration model	Exposure-age-duration model
Females		
Smokers <sup>b</sup>	0.013	0.0086
Nonsmokers	0.030	0.020
Males		
Smokers <sup>b</sup>	0.012	0.0079
Nonsmokers	0.028	0.019

<sup>a</sup> Based upon results (Table 3-7 in BEIR VI) for the submultiplicative model for smoking and radon and exposures of 6.3–41 WLM in 70 years.

<sup>b</sup> Category includes current and former smokers (“ever-smokers” in BEIR VI).

The empirical models of BEIR VI provide by far the most sophisticated estimates of the lung cancer risks attributable to low level exposure to radon progeny to date. The fit of the E-A-C model to the miner data indicates that, at levels of exposure of interest around Rocky Flats, the concentration modifying factor, which accounts for the enhancement of lung cancer production for protracted exposures, is at its maximum value of 1. Use of the BEIR VI relative risk approach for estimating risks of lung cancer requires baseline lung cancer risk estimates for the exposed population. Those data and the application of the BEIR VI results to plutonium exposures around Rocky Flats are discussed in [Section 7.1.3](#).

### 7.1.3 Applying BEIR VI Risk Estimates to Rocky Flats Plutonium Exposures

The distribution of doses to tissues in the lung is not the same for radon progeny and the long-lived plutonium isotopes. For radon progeny, the doses to the bronchial epithelium are about seven times larger than those to the pulmonary (or alveolar interstitial) tissue. For plutonium, the dose distribution is more uniform: the average absorbed dose to the lungs is estimated to be about three-fourths of the absorbed dose to the basal and secretory cells in the bronchial and bronchiolar regions ([ICRP 1994](#)). In spite of differences between exposures to radon progeny and to plutonium, risk estimates for radon were used as a basis for risk estimates for plutonium in the BEIR IV report ([NAS/NRC 1988](#)).

[Gilbert et al.](#) (1992) compared results of studies of lung cancer in rats exposed to high doses from inhalation of radon progeny and of <sup>239</sup>Pu dioxide. The tumor types produced by the two contaminants differed. Exposure to radon progeny led primarily (46%) to adenocarcinomas with an additional 16% of the total number of tumors due to adenomas. Only 26% of the tumors induced by radon progeny were epidermoid/squamous cell carcinomas. Plutonium exposure produced primarily (50%) the latter type and only about 26% adenocarcinomas. Fewer than 3% of the plutonium-induced tumors were adenomas.

[Gilbert et al.](#) (1992) found that the total radiogenic tumor risks from plutonium and radon progeny were comparable at the lowest dose levels (1–2 Gy or 100–200 rad). Although the details of tumor production and their relationship to dose distribution are not understood, we believe that it is reasonable to use radon risk estimates to estimate lung cancer risks for

plutonium exposures. Our approach, which uses the E-A-C model of BEIR VI to estimate plutonium risks, is described in this section.

Estimates of several parameters are needed to apply the BEIR VI model to plutonium and each parameter adds some uncertainty to the result. We estimate excess relative risk coefficients for plutonium exposure of smokers and nonsmokers ( $\beta_{Ps}$  and  $\beta_{Pn}$ ,  $\text{mGy}^{-1}$ ) from the central relative risk coefficient for radon exposure ( $\beta_R$ ,  $\text{WLM}^{-1}$ ) using the following equations:

$$\beta_{Ps} = \frac{\beta_R}{DF_R} K \phi_s \phi_m \quad (7-1)$$

$$\beta_{Pn} = \frac{\beta_R}{DF_R} K \phi_n \phi_m \quad (7-2)$$

where  $DF_R$  is the dose factor for radon progeny exposure ( $\text{mGy WLM}^{-1}$ ),  $K$  is a dosimetry transfer uncertainty factor that reflects differences in dose per unit exposure in mines and in other environments, the parameters  $\phi_s$  and  $\phi_n$  are risk modifying factors for smokers and nonsmokers, respectively, and  $\phi_m$  is a modeling uncertainty factor that reflects the differences between predictions of the two BEIR VI models (see [Table 7-2](#)). The BEIR VI assessments of the parameters  $\beta_R$ ,  $DF_R$ , and  $K$  were discussed in [Section 7.1.2](#). The risk modifying factors  $\phi_s$  and  $\phi_n$  are derived from the BEIR VI analysis of the effects of smoking status in groups of miners for which this information was available. Excess relative risks per WLM for the smokers ( $\beta_s$ ), nonsmokers ( $\beta_n$ ), and for all miners without regard to smoking status ( $\beta_a$ ) were estimated and used to compute the modifying factors for smoking status. The relationships are shown in the following equations.

$$\phi_s = \frac{\beta_s}{\beta_a} \quad (7-3)$$

$$\phi_n = \frac{\beta_n}{\beta_a} \quad (7-4)$$

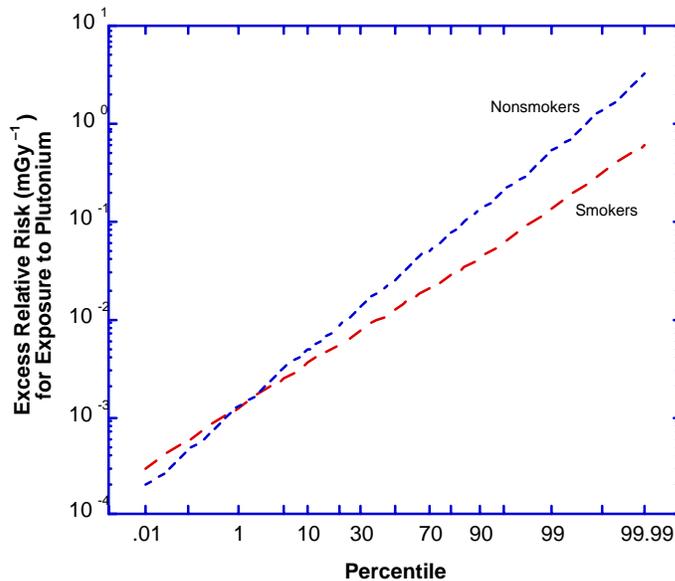
The three risk parameters ( $\beta_s$ ,  $\beta_n$ ,  $\beta_a$ ) were approximately lognormally distributed. The uncertainty distributions for the risk modifying factors ( $\phi_s$ ,  $\phi_n$ ) which were also approximately lognormally distributed, and the other parameters ( $\beta_R$ ,  $DF_R$ ,  $K$ ,  $\phi_m$ ), are summarized in [Table 7-3](#).

Monte Carlo calculations have been performed to estimate the distributions of excess relative risks for smokers and nonsmokers using Equations [7-1](#) and [7-2](#) and the parameter distributions in [Table 7-3](#). Results of these calculations are presented in [Figure 7-1](#). The estimated GM and GSD for  $\beta_{Ps}$ , the risk coefficient ( $\text{mGy}^{-1}$ ) for smokers, are  $0.0123 \text{ mGy}^{-1}$  and 2.75, respectively. For nonsmokers, the distribution parameter estimates for  $\beta_{Pn}$  ( $\text{mGy}^{-1}$ ) are  $0.0257 \text{ mGy}^{-1}$  and 3.85, respectively. The estimated risk coefficient for nonsmokers is larger than that for smokers; however, the risks to smokers are higher because their baseline lung cancer rates (discussed below) are higher. The larger uncertainty in the risk coefficient for nonsmokers is due to the large uncertainty in the risk modifying factor for nonsmokers ( $\phi_n$ ). The GSD for its lognormal distribution is 3.02 ([Table 7-3](#)).

**Table 7-3. Distributions of Parameters Used to Estimate Risk Factors  
for Plutonium Exposure of Smokers and Nonsmokers**

Parameter	Unit	Uncertainty Distribution
Excess relative risk for radon exposure, $\beta_R$	WLM <sup>-1</sup>	Lognormal (0.077, 1.36) <sup>a</sup>
Dose coefficient for radon progeny, $DF_R$	mGy WLM <sup>-1</sup>	Uniform (2.5–6.1) <sup>b</sup>
Dosimetry transfer uncertainty factor, $K$	none	Lognormal (1.0, 1.65) <sup>a</sup>
Risk modifying factor for smokers, $\phi_s$	none	Lognormal (0.91, 2.00) <sup>a</sup>
Risk modifying factor for nonsmokers, $\phi_n$	none	Lognormal (1.92, 3.02) <sup>a</sup>
Modeling uncertainty factor, $\phi_m$	none	Uniform (0.5–1.0) <sup>b</sup>

<sup>a</sup> (Geometric mean, geometric standard deviation) for lognormal distribution.  
<sup>b</sup> (Lower bound, upper bound) for uniform distribution.

**Figure 7-1.** Estimated excess relative risks ( $\text{mGy}^{-1}$ ) for smokers and nonsmokers who have inhaled plutonium; estimates based upon BEIR VI relative risk models for radon progeny.

Applying these estimates of excess relative risks requires information about the baseline lung cancer risks in particular population groups. Data on lung cancer death rates in Colorado for the period 1980–1997 were provided by the Health Statistics Section of the CDPHE and are presented in [Table 7-4](#). For some young age categories no deaths were recorded and estimates based on national statistics are used.

The data in [Table 7-4](#) were used to derive estimates of the baseline risks for smokers and nonsmokers of both genders. The underlying assumptions for these calculations are the same as used in the BEIR VI report. They are: (1) relative risks of lung cancer for smokers ( $RR_s$ ) are 14 and 12 compared with nonsmokers for males and females, respectively, and (2) the proportions ( $P_s$ ) of smokers in the population are 0.58 and 0.42 for males and females, respectively. It was estimated that 95% and 90%, of all lung cancer deaths occur in male and female smokers,

respectively, and those estimates were found to be consistent with recent data (NAS/NRC 1998). If  $r_o(a)$  is the overall lung cancer mortality rate in a particular age group, then the lung cancer mortality rate for nonsmokers in that group,  $r_n(a)$ , is estimated using:

$$r_n(a) = \frac{r_o(a)}{([1 - P_s] + RR_s P_s)} \quad (7-5)$$

This equation is not used to estimate baseline lung cancer risks for persons under age 25. For our analysis, the baseline lung cancer rates for those persons is not considered to be affected by smoking status.

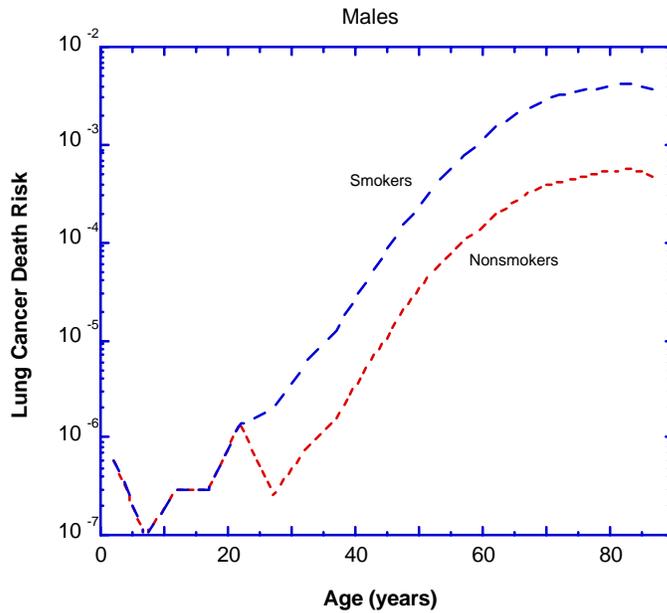
**Table 7-4. Age Specific Lung Cancer Mortality Rates for Colorado for the Period 1980–1997**

Age (y)	Lung cancer mortality (per thousand)	
	Males	Females
0–4	0.0006 <sup>a</sup>	0.0004 <sup>a</sup>
5–9	0.0001 <sup>a</sup>	0.0004 <sup>a</sup>
10–14	0.0003 <sup>a</sup>	0.0003 <sup>a</sup>
15–19	0.0003 <sup>a</sup>	0.0002 <sup>a</sup>
20–24	0.0014 <sup>a</sup>	0.0002 <sup>a</sup>
25–29	0.0022	0.0022
30–34	0.0062	0.0037
35–39	0.0138	0.0121
40–44	0.0480	0.0356
45–49	0.150	0.127
50–54	0.414	0.309
55–59	0.892	0.514
60–64	1.723	0.990
65–69	2.770	1.320
70–74	3.607	1.735
75–79	4.286	1.862
80–84	4.739	1.791
85+	4.081	1.311

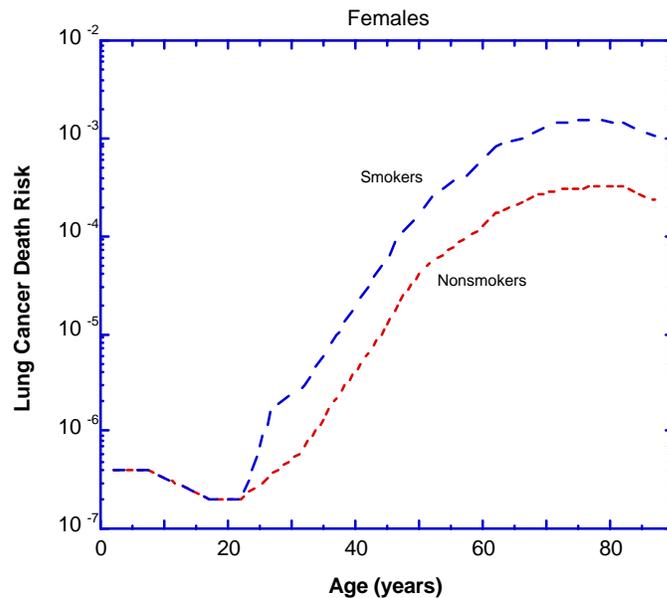
<sup>a</sup> No lung cancer deaths observed. Rates are from national statistics for 1980–1984 (NAS/NRC 1988).

Figures 7-2 and 7-3 present the computed baseline risk rates for males and females using the data for the Colorado population in Table 7-4. The long interval (1980–1997) was used to obtain more reliable estimates; it is recognized that the rates were not constant throughout the period. Baseline lung cancer risks for ages under 25 years are quite small and those for ages under 50 years are relatively small (<0.2 per thousand). This means that cumulative baseline risks are virtually the same for persons aged 0–49 years. The lung cancer risks from inhalation of plutonium are proportional to the cumulative baseline risks and are therefore practically independent of age at exposure over that interval. The cumulative baseline risks of lung cancer to age 85 and beyond for males were estimated, using the data in Table 7-4, to be  $1.3 \times 10^{-2}$  for

nonsmokers and  $1.0 \times 10^{-1}$  for smokers. Similarly, the estimated cumulative baseline risks of lung cancer for female nonsmokers and smokers are somewhat less,  $8.9 \times 10^{-3}$  and  $4.1 \times 10^{-2}$ , respectively.



**Figure 7-2.** Estimated mean baseline lung cancer death risks for male smokers and nonsmokers in Colorado, 1980–1997 (data for the U.S. were used for ages less than 25 years.)



**Figure 7-3.** Estimated mean baseline lung cancer death risks for female smokers and nonsmokers in Colorado, 1980–1997 (data for the U.S. were used for ages less than 25 years.)

These results are not believed to be representative of the cumulative baseline risks for groups around Rocky Flats during years when the largest releases occurred because lung cancer deaths have been increasing with time. Data for the U.S. during the period 1930–1986, provided in the BEIR VI report, show a continual increase in lung cancer risk for males during that period. The increase for females was not as dramatic for years before 1960, but the percentage increase for females has been greater in recent years than that for males. *The rates in the decade 1960–1970, which approximates the periods of largest exposures around Rocky Flats, are estimated to be 1–1.5 times lower for men and 3–4 times lower for women than those shown in Figures 7.2 and 7.3.*

The BEIR VI models both employ age modifying factors that account for a decrease in excess relative risk with increasing age. Four age categories are defined: 0–54 y, 55–64 y, 65–74 y, and  $\geq 75$  y. The age modifying factors for the E-A-C model from BEIR VI and the baseline risks for these periods are shown in Table 7-5.

**Table 7-5. Age Modifying Factors for BEIR VI Exposure-Age-Concentration Model and Cumulative Baseline Lung Cancer Risks for BEIR VI Age Categories**

Age range (years)	Age modifying factor <sup>a</sup> for the E-A-C model of BEIR VI	Cumulative baseline lung cancer risks			
		Males		Females	
		Nonsmokers	Smokers	Nonsmokers	Smokers
0–54	Lognormal (1.0, 1.1) <sup>a</sup>	$3.8 \times 10^{-4}$	$2.8 \times 10^{-3}$	$4.4 \times 10^{-4}$	$2.0 \times 10^{-3}$
55–64	Lognormal (0.57, 1.27)	$1.5 \times 10^{-3}$	$1.2 \times 10^{-2}$	$1.3 \times 10^{-3}$	$6.2 \times 10^{-3}$
65–74	Lognormal (0.29, 1.39)	$3.7 \times 10^{-3}$	$2.8 \times 10^{-2}$	$2.7 \times 10^{-3}$	$1.3 \times 10^{-2}$
$\geq 75$	Lognormal (0.09, 2.55)	$7.7 \times 10^{-3}$	$5.7 \times 10^{-2}$	$4.4 \times 10^{-3}$	$2.0 \times 10^{-2}$

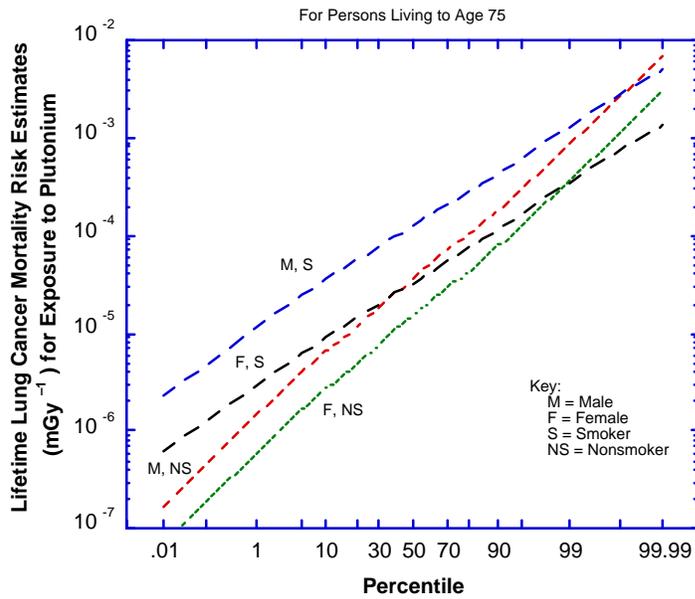
<sup>a</sup> (Geometric mean, geometric standard deviation) for lognormal distribution shown.

The gender-specific excess relative risks of lung cancer per unit dose for smokers ( $ERR_s$ ) and for nonsmokers ( $ERR_n$ ) in particular age categories are estimated using the following equations:

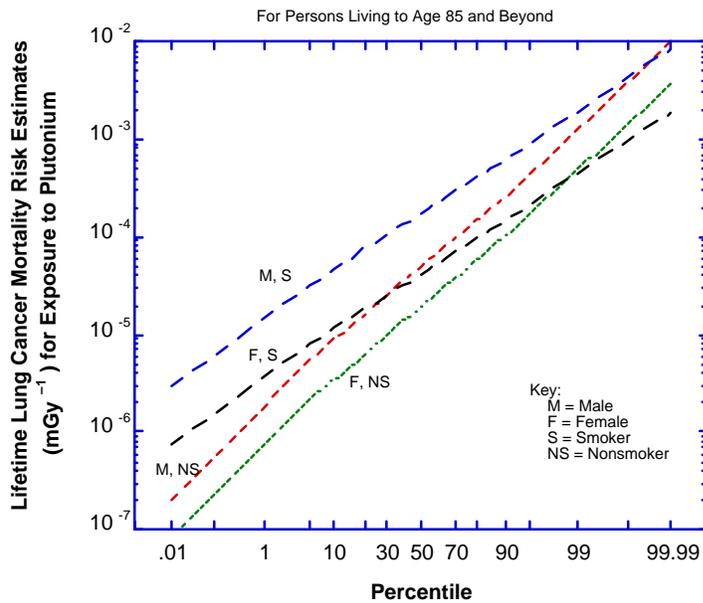
$$ERR_s = \beta_{Ps} \phi_a R_{Bs} \phi_T \quad (7-6)$$

$$ERR_n = \beta_{Pn} \phi_a R_{Bn} \phi_T \quad (7-7)$$

In these equations:  $\beta_{Ps}$  ( $\text{mGy}^{-1}$ ) and  $\beta_{Pn}$  ( $\text{mGy}^{-1}$ ) are the excess relative risk coefficients (Equations 7-1 and 7-2, Figure 7-1) for smokers and nonsmokers exposed to plutonium, respectively;  $\phi_a$  is the appropriate lognormally distributed age modifying factor (Table 7-5);  $R_{Bs}$  and  $R_{Bn}$  are the cumulative baseline lung cancer risks for smokers and nonsmokers in the age category, respectively (Table 7-5); and  $\phi_T$  is a modifying factor that reflects changes in the baseline risk between the time when the most significant exposures occurred and the period (1980–1997) used to derive the baseline risks. The cumulative baseline risks and the corresponding modifying factor ( $\phi_T$ ) are the gender-specific parameters in these calculations. The estimated ranges of  $\phi_T$  for males and females were stated above.



**Figure 7-4.** Estimated lifetime lung cancer mortality risks (mGy<sup>-1</sup>) for persons inhaling plutonium and living to age 75.



**Figure 7-5.** Estimated lifetime lung cancer mortality risks (mGy<sup>-1</sup>) for persons inhaling plutonium and living to age 85 and beyond.

The risks per unit dose from plutonium for smokers and nonsmokers of both genders and the associated uncertainty distributions have been estimated using Monte Carlo techniques. The distributions of risk estimates for plutonium-induced lung cancer in persons living to age 75 are presented in [Figure 7-4](#) and those for the relatively few persons who live to age 85 and beyond are shown in [Figure 7-5](#). All distributions include a broad range of estimates. The GSDs for the distributions of risk factors for smokers of either gender are in the range 2.8–2.9. For nonsmokers, the estimated risk factors are characterized by even larger GSDs (3.9–4.0). Median risk estimates for smokers clearly exceed those for nonsmokers. However, because the GSDs are so large, the upper bound risk factors for nonsmokers are estimated to exceed those for smokers. These larger GSDs are due primarily to the large uncertainty (GSD = 3.02) associated with the modifying factor for excess relative risk for nonsmokers ([Table 7-3](#)).

#### 7.1.4 Summary

There have been several estimates of the risks of lung cancer from radon exposure in the past 20 years. The recently published BEIR VI analyses of the data are the most sophisticated to date. In spite of differences in dose distribution and in types of tumors produced, animal experiments indicate that the overall cancer risks due to inhalation of plutonium or radon progeny are comparable at the low doses of interest in this study. The preferred relative risk models for radon from the BEIR VI report were chosen as the basis for estimating the risks of plutonium-induced lung cancer.

In the BEIR VI preferred approach, the interaction of smoking and radon exposure is estimated to be submultiplicative and risks are estimated for both smokers and nonsmokers. However, the modifying factor for the excess relative risks for nonsmokers is one of the largest uncertainties in the model.

Baseline lung cancer mortality risks for both genders and for smokers and nonsmokers were derived from lung cancer statistics for the State of Colorado. The effects of exposure level, age, and dosimetric differences are addressed and the associated uncertainties are included in the Monte Carlo calculations of risk estimates for plutonium inhalation exposure. The estimated risk factors are characterized by rather broad distributions as shown in [Table 7-6](#), which summarizes the results.

## 7.2 Risk Estimates for Liver

Solutions of colloidal thorium dioxide (Thorotrast) used as contrast agents in medical radiography were injected into patients in several countries. Natural thorium is radioactive and consists primarily of  $^{232}\text{Th}$ , a very long-lived (14-billion year half-life) alpha-emitter that is the parent of a long sequence of radioactive nuclides (see [Glossary](#)). Other alpha-emitters in the chain following  $^{232}\text{Th}$  decay are  $^{228}\text{Th}$ ,  $^{224}\text{Ra}$ ,  $^{220}\text{Rn}$ ,  $^{216}\text{Po}$ ,  $^{212}\text{Bi}$ , and  $^{212}\text{Po}$ . All of these radionuclides contribute to the doses received from Thorotrast injections.

**Table 7-6. Lifetime Lung Cancer Mortality Risk Estimates  
Following Inhalation Exposure to Plutonium**

Population exposed	Estimated lifetime lung cancer mortality risks (Gy <sup>-1</sup> )			
	Persons living to age 75		Persons living to age 85 and beyond	
	GM <sup>a</sup>	GSD <sup>a</sup>	GM <sup>a</sup>	GSD <sup>a</sup>
Females				
Smokers <sup>b</sup>	0.033	2.8	0.041	2.8
Nonsmokers	0.015	3.9	0.020	3.9
Males				
Smokers <sup>b</sup>	0.13	2.8	0.17	2.9
Nonsmokers	0.036	3.9	0.050	4.0
Mixed	0.063	2.6	0.085	2.7

<sup>a</sup> GM is the geometric mean of the lognormal distribution, and GSD is its geometric standard deviation.

<sup>b</sup> Category includes current and former smokers (“ever-smokers” in BEIR VI).

The colloidal thorium and its decay products were deposited in several tissues following injection. The distribution for a “standard patient” in the German cohort was given by [Kaul and Noffz](#) (1978) as liver (59%), spleen (29%), red bone marrow (9%), calcified bone (2.4%), lungs (0.7%), and kidneys (0.1%). Average annual dose estimates (to standard man) were given in the paper for various injection volumes. For an average injection of 25 mL of solution, the mean dose rate to the liver was estimated to be 0.24 Gy y<sup>-1</sup> (24 rad y<sup>-1</sup>) ([Kaul and Noffz](#) 1978). A typical injection of 25 mL of Thorotrast contained about 5 grams of thorium (20 kBq <sup>232</sup>Th), plus additional radioactivity from its decay products ([Mays](#) 1982) (see [Glossary](#) also). Because the thorium is in colloidal form, the dose to a tissue is not necessarily uniformly distributed throughout the tissue as implied by the average dose rate. However, the specific cells in the liver that are sensitive to the induction of liver cancer are not known. Animal and other studies (see [Section 8.2.3](#)) indicate that the liver cancers induced by Thorotrast are the result of its radioactivity and not due to the mass of the colloidal material or to chemical effects of the Thorotrast.

**A typical injection was ~25 mL of Thorotrast, containing ~5 grams of thorium and ~0.55 μCi of the alpha-emitter <sup>232</sup>Th.**

[Kathren and Hill](#) (1992) have estimated doses to some tissues in an autopsied female patient who had received a Thorotrast injection (~25 mL) about 36 years before death. Average annual dose rate estimates for this patient were estimated to be 0.42 Gy y<sup>-1</sup> (42 rad y<sup>-1</sup>) for the liver. [Hunacek and Kathren](#) (1995) reported dose estimates based on a second autopsy for which the estimated dose rate was 0.13 Gy y<sup>-1</sup> (13 rad y<sup>-1</sup>) to the liver. The mean liver dose rate based upon the autopsy data was 0.28 Gy y<sup>-1</sup> (28 rad y<sup>-1</sup>), slightly higher than the dose rate of 0.24 Gy y<sup>-1</sup> given by [Kaul and Noffz](#) (1978).

The BEIR IV report discusses five epidemiologic studies of persons who were exposed to Thorotrast. These populations were located in Germany, Japan, Portugal, Denmark, and the United States. Risk estimates for a linear model of liver cancer induction were derived from three of the studies by the BEIR IV Committee. The three estimates were very consistent. Estimates for the German, Japanese, and Portuguese cohorts were 300, 260, and 280 liver cancers per 10<sup>4</sup>

P-Gy (or per  $10^6$  P-rad), respectively ([NAS/NRC 1988](#)). Recent papers on the findings for the Danish cohort of patients were summarized in [UNSCEAR \(1994\)](#). The liver cancer risk estimate for that group is about 700 cases per  $10^4$  P-Gy (or per  $10^6$  P-rad) ([Andersson et al. 1994](#)).

Using the new dose estimates based upon the whole body autopsy cited above, [Hunacek and Kathren \(1995\)](#) made estimates of the risk coefficient for liver cancer in the German, Japanese, and Portuguese studies. They weighted the results using the numbers of cases found in the studies and computed a weighted mean risk coefficient of 200 fatal liver cancers per  $10^4$  P-Gy (or per  $10^6$  P-rad). Individual estimates for the three cohorts were 230, 350, and 100 fatal liver cancers per  $10^4$  P-Gy (or per  $10^6$  P-rad) for the German, Japanese, and Portuguese groups, respectively. Hunacek and Kathren did not perform an independent analysis of the risk estimate for the Danish cohort. They considered the Danish data to be less reliable because the rates were compared to population statistics rather than to those for a matched control group.

The results of various analyses of the risk factor for liver cancers caused by Thorotrast cover a broad range, 100–700 fatal cancers per  $10^4$  P-Gy. Before applying these results to estimate liver cancer risks from plutonium, there are several factors to consider. There are uncertainties in dosimetry, discussed above. Because of differences in chemical forms, it could be anticipated that there are differences in the distributions of colloidal thorium and plutonium deposited in the liver. Taking these factors into account, we adopt a most likely value of the liver cancer mortality risk coefficient of  $3 \times 10^{-2} \text{ Gy}^{-1}$  and estimate the bounds on this estimate to be  $0.5 \times 10^{-2} \text{ Gy}^{-1}$  to  $15 \times 10^{-2} \text{ Gy}^{-1}$ . A log-triangular distribution is used because of the broad range of estimates.

### 7.3 Risk Estimates for Bone (Endosteal Cells)

Because the history of risk estimates for bone has been somewhat confused, Section 7.3.1 addresses the need for consistency between risk coefficients and dose estimates. Sections [7.3.2](#) through [7.3.4](#) discuss the three sources of risk estimates for bone cancer that are based upon exposure to alpha-emitters other than plutonium. [Section 7.3.5](#) briefly discusses risk estimates for bone cancer that were based on radium and plutonium exposures in both animals and man. [Section 7.3.6](#) summarizes the results of the various studies and contains risk estimates for plutonium-induced bone cancers.

#### 7.3.1 Consistency between Dose Estimates and Risk Coefficients

Consistency between bone dosimetry and risk coefficients (risks per unit dose) used to estimate numbers of bone cancers is essential ([Puskin et al. 1992](#); [Bair and Sinclair 1992](#)). Historically, detailed knowledge of the development of radiation-induced cancers was not available. In the absence of such information, average radiation doses were computed for tissues at risk. One of the first bone-seeking radionuclides studied in detail was radium (mainly  $^{226}\text{Ra}$  with some  $^{228}\text{Ra}$ ) ingested by dial painters. The radium behaved much like calcium and was distributed throughout the bone. In studies of bone cancer resulting from those intakes, average skeletal doses to exposed persons were used to derive risk estimates. Estimates in the BEIR IV report ([NAS/NRC 1988](#)), for example, refer to average skeletal dose from radium.

As the knowledge base about radiation-induced bone cancer increased, attention was focused on the endosteal cells that line bone surfaces as the cells at risk for cancer development. Initially, plutonium deposits on bone surfaces and, although the distribution changes with time,

doses to bone surfaces are estimated to be high. This is found even for exposures to aerosols like plutonium dioxide that are slowly cleared from the lung. Techniques were developed to estimate doses to those cells and doses to “bone surfaces” are now commonly calculated. Average skeletal doses are no longer estimated routinely (ICRP 1989a, 1995a).

To compute the lifetime risk of bone cancer following an intake of plutonium, the risk factor selected must be consistent with the tissue dose estimate. It is inappropriate to use dose estimates for bone surfaces together with a cancer risk coefficient that was derived using estimates of average skeletal dose (or vice versa). If one chooses a lifetime risk coefficient based upon average skeletal dose ( $RC_s$ ) then the calculation of risk ( $R$ ) must employ the average skeletal dose ( $D_s$ ) to the exposed group. That is,  $R = D_s \times RC_s$ . Alternatively, the lifetime risk coefficients for the endosteal cells ( $RC_e$ ) could be used with the dose to that tissue ( $D_e$ ). For that choice,  $R = D_e \times RC_e$  is also an appropriate calculation.

### 7.3.2 Estimates from Studies of Dial Painters Ingesting $^{226}\text{Ra}$ and $^{228}\text{Ra}$

Much of the early knowledge of the effects of alpha emitters in humans came from the study of radium dial painters, or luminizers as they have also been called. Mostly young women, they ingested substantial quantities of radium because of the practice of orally tipping their brushes while painting with a radium solution to make dials luminous. Their radium intakes consisted primarily of the two long-lived isotopes  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ , whose half-lives are 1600 and 5.75 years, respectively. Over time, the long-lived radium isotopes became more uniformly distributed throughout the bone volume of the dial painters. As a result, the dose from these isotopes is delivered to the entire bone mass, rather than to cells near bone surfaces.

Failure to observe bone cancers in the groups of luminizers who received lower doses led to the idea of a practical threshold (near 10 Gy [1000 rad] mean skeletal dose) for bone cancer induction (Evans 1974). Rowland et al. (1983) examined various dose-response relationships to fit the dial painter cancer data. The most general form of the dose response curves was a linear-quadratic exponential (L-Q-E) equation:

$$I = (C + aD + bD^2)e^{-cD} \quad (7-8)$$

where  $I$  is the incidence of bone sarcoma per person-year of exposure and  $D$  is the radium intake (or could be the mean bone dose derived from the radium intake). In Equation (7-1),  $C$  refers to the natural incidence, which is quite low,  $\sim 10^{-5} \text{ y}^{-1}$ . The parameters  $a$  and  $b$  are fitting constants for the terms proportional to dose (the linear term) and to the square of the dose (the quadratic term), respectively. The parameter  $c$  is the fitting constant for the exponential term. Inclusion of the negative exponential term allows the model to fit the observed decrease in bone sarcoma risk for average skeletal doses above about 100 Gy (10,000 rad). The fit of functions of this or any other type to the data is controlled by the observations at high dose levels; extrapolation to low doses, outside the range of observed effects, is highly uncertain.

In a recent review of results for American dial painters, Thomas (1994) stated that in the approximately 1400 luminizers with doses estimated to be below 10 Gy (1000 rad), no cancers had been observed. His analysis of the data for this group suggests a threshold in the range of 4–6 Gy, somewhat lower than that suggested by Evans. Thomas’ analysis was limited to female dial painters from the U.S. Male dial painters and those exposed in other ways were not included.

[Mays](#) (1988) stated that there have been six skeletal cancers in persons from the U.S. and U.K. whose skeletal doses ranged from 0.85 to 12 Gy (85 to 1200 rad). He identifies three bone sarcomas at doses of 8.9 Gy (890 rad), 4.6 Gy (460 rad), and 0.85 Gy (85 rad). The latter two were dial painters, one British. The person with the highest dose drank a radium solution. Mays identified three head sinus carcinomas at doses of 11.8, 7.1, and 1.2 Gy (1180, 710, and 120 rad). The first two were dial painters; the last person drank a radium solution. These cases suggest that if there is a practical threshold it must be nearer 1 Gy (100 rad) than 10 Gy (1000 rad). However, [Thomas](#) (1994) suggests that, if newer methods were used, the doses for these persons would be higher than reported previously. It is not clear whether the doses would exceed his estimates of threshold dose for bone cancer.

[Schlenker](#) (1982) analyzed the uncertainty in the risk estimates at low doses and showed that they were quite large. For a cumulative 50-year endosteal dose ( $D_e$ ) of 0.75 Gy (75 rad), the predicted excess bone sarcoma incidence is less than one-half the natural incidence rate which is  $10^{-5} \text{ y}^{-1}$ . The 95% confidence interval includes a range from no excess incidence to ~10 times the expected value. The central estimate corresponds to a risk coefficient ( $RC_e$ ) of about 4 cancers per  $10^4$  P-Gy (4 per  $10^6$  P-rad).

A linear fit to the same data was also performed ([Mays and Lloyd](#) 1972). Their estimate of the risk was 46 bone sarcomas per  $10^4$  P-Gy (or per  $10^6$  P-rad) which is ten times the value reported by [Schlenker](#) (1982) and five times the natural incidence. Because of the large extrapolation, this estimate must also be considered very uncertain. The visual contrast between graphic presentations of the alternative approaches (practical threshold, linear fit, L-Q-E model) to the data is striking (see page 198 in [NAS/NRC](#) 1988).

The analysis in [Raabe et al.](#) (1980) examined the effects of time to death and dose rate on the risk function for radium-induced bone cancer. They found good correlations in dose response between studies in animals and humans when accounting for the differing lifespans. This model also implies that there is a dose below which no effect will be seen. For bone cancer induction by  $^{226}\text{Ra}$ , a threshold dose of 0.8 Gy (80 rad) was estimated ([Raabe](#) 1983).

### 7.3.3 Patients Treated with $^{224}\text{Ra}$

Two groups of German patients, persons (including children) with tuberculosis and adults with ankylosing spondylitis, received internal radiation therapy treatments that employed  $^{224}\text{Ra}$ . This short-lived (3.66-day half-life) radium isotope delivers most of its dose while still close to endosteal tissues. Therefore, for dosimetry, it is considered to be more similar to plutonium than to  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ . Data from the longest study, which began in 1952, have been analyzed in several papers, some of which are discussed below. The BEIR IV report ([NAS/NRC](#) 1988) gives more details.

Most of the analyses have been done in terms of average skeletal dose ( $D_s$ ), although [Mays](#) (1982) gave an estimated linear risk coefficient ( $RC_e$ ) of 27 cases per  $10^4$  P-Gy (27 cases per  $10^6$  P-rad) to the endosteal tissue for the  $^{224}\text{Ra}$  patients. An analysis in [Mays and Spiess](#) (1983) yielded risk coefficients ( $RC_s$ ) for juveniles and adults of  $188 \pm 32$  and  $133 \pm 36$  bone sarcomas per  $10^4$  P-Gy, respectively. The BEIR IV Committee, taking dose protraction into account, gave a risk estimate ( $RC_s$ ) for a linear model of 200 bone sarcomas per  $10^4$  P-Gy (200 bone sarcomas per  $10^6$  P-rad) for exposure to  $^{224}\text{Ra}$  ([NAS/NRC](#) 1988).

A more recent analysis by [Chmelevsky et al.](#) (1986) led to a rejection of an attempt to fit the data using a linear dose-response model. No differences were seen between juvenile and adult

groups and the pooled data were used to derive an L-Q-E dose response relationship. The risk of a tumor per P-Gy for an average skeletal dose of less than 1 Gy (100 rad) and a 25-year expression period was estimated to be

$$RC_s = (0.0085D_s + 0.0017D_s^2)e^{-0.025D_s} \quad (7-9)$$

where  $D_s$  is the average skeletal dose (Gy). Based on a 1988 analysis, [Mays](#) (1989) gave a slightly different equation:

$$RC_s = (0.0083D_s + 0.0019D_s^2)e^{-0.027D_s} \quad (7-10)$$

which predicted more cancer cases (six) than had been seen (two) in the second, lower dose, group of patients injected with  $^{226}\text{Ra}$ . Continued attention to that group, which had an average follow-up time of only 16 years (compared with 24 years for the higher dose group) was recommended ([Mays](#) 1989). For an average skeletal dose of 1 Gy, [Equation \(7-10\)](#) yields an estimated risk coefficient ( $RC_s$ ) of  $1 \times 10^{-2} \text{ Gy}^{-1}$ . For an average skeletal dose of 0.1 Gy,  $RC_s$  is estimated to be  $0.085 \times 10^{-2} \text{ Gy}^{-1}$ .

### 7.3.4 Thorotrast Patients

Patients exposed to the colloidal thorium oxide preparation called Thorotrast have been primarily identified as a source of information about liver cancer induced by alpha-emitting radionuclides. As discussed in [Section 7.2](#), several alpha-emitting radionuclides contribute to the doses from this preparation. Other cancers besides those in the liver have been observed during follow up of these patients and the data have been used to develop other risk estimates, including one for bone cancer.

In their evaluation of the distribution of Thorotrast in the exposed persons, [Kaul and Noffz](#) (1978) identified 9% of the material as being in bone marrow and 2.4% in calcified bone of the “standard patient.” Uniform concentrations of the radionuclides have generally been assumed, but this was not necessarily the case for the colloidal material. Average dose rates to endosteal surfaces of bone were estimated to be about  $0.12 \text{ Gy y}^{-1}$  ( $12 \text{ rad y}^{-1}$ ) for the average injection volume of 25 mL ([Kaul and Noffz](#) 1978). [Mays](#) (1978) estimated that the endosteal dose rate ( $D_e$ ) was  $0.16 \text{ Gy y}^{-1}$  ( $16 \text{ rad y}^{-1}$ ).

Using whole body autopsy results, [Kathren and Hill](#) (1992) estimated an average skeletal dose rate ( $D_s$ ) of  $0.11 \text{ Gy y}^{-1}$  ( $11 \text{ rad y}^{-1}$ ) for a female patient who had received about 25 mL of Thorotrast 36 years before death. Their estimates were based upon laboratory analyses of many tissues containing the long-lived alpha-emitting nuclides from the thorium chain that were present at the time of death.

Based on [Mays and Spiess](#) (1979), the BEIR IV Committee gave an estimate ( $RC_s$ ) of 55–120 bone cancers per  $10^4$  P-Gy (55–120 bone cancers per  $10^6$  P-rad) for a linear model. Using the new dose estimates based upon the whole body autopsy data cited above, [Hunacek and Kathren](#) (1995) made estimates of  $RC_s$  for bone cancer in the German, Japanese, and Portuguese study populations. Their estimates are 9, 50, and 33 fatal cancers per  $10^4$  P-Gy for these groups, respectively. They weighted the results using the numbers of cases found in the studies and computed a weighted mean risk coefficient ( $RC_s$ ) of 20 bone cancers per  $10^4$  P-Gy (or per  $10^6$  P-

rad). The difference between these and previous estimates is due primarily to differences in dosimetry based upon the whole body autopsy results.

### 7.3.5 Bone Cancer Induction by Radium and Plutonium in Animals and Man

For plutonium, the BEIR IV Committee ([NAS/NRC 1988](#)) adopted a bone cancer risk estimate based on a meta-analysis, using a linear dose-response model, of results from 13 human and animal studies of cancer following skeletal deposition of radium and plutonium. Included were the human radium exposure experience and limited data from human plutonium studies; beagle injection and inhalation studies (at the University of Utah, at the Inhalation Toxicology Research Institute, Albuquerque, and at Hanford); and rat inhalation studies. This analysis was also published separately by [DuMochel and Groër \(1989\)](#). A brief discussion of this analysis was included in this chapter for completeness. However, because it was largely based upon results from animal experiments, it does not truly fall in the category of risk estimates being discussed here.

The central (median) risk coefficient ( $RC_s$ ) derived for plutonium-produced bone cancer was 300 bone cancers per  $10^4$  P-Gy (or per  $10^6$  P-rad). The range of  $RC_s$  values was 80 to 1100 bone cancers per  $10^4$  P-Gy. These were reported as deaths ([NAS/NRC 1988](#)). The distinction between incidence and mortality is not clear, however, because in the case of the animals the two are virtually the same since they received no therapy. The range of estimates represents the 95% confidence interval for the median estimate and indicates the magnitude of the uncertainties when predicting risks at low doses. They concluded that, given the information available, there was not much hope of reducing the uncertainty in the risk coefficient below about a factor of 4 in either direction ([DuMochel and Groër 1989](#)).

### 7.3.6 Summary

There are several sources of estimates of risk coefficients for the skeleton and for endosteal cells on bone surfaces based upon previous human experience with alpha emitters other than plutonium. One of the largest uncertainties in these estimates, summarized in [Table 7-7](#), is the extrapolation from effects observed at high doses to those expected at low doses. This is particularly an issue for the results for the radium dial painters exposed to  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ . The differences between results for different models of their cancer risk were discussed above. However, when considering environmental levels of plutonium, the problem of low dose extrapolation applies to the other estimates as well.

The original risk coefficient estimates in [Table 7-7](#) were for bone cancer incidence. Some results of later analyses were stated to be risks of death; however, there seems not to have been any adjustment for the outcome of cancer treatment. The focus on incidence was typical of the analyses of radium dial painter data and was carried along to analyses of risks from other agents. Treatment was not a component of the animal studies.

Only two of the estimates in [Table 7-7](#) were for  $RC_e$ , which is the most useful quantity for this plutonium risk assessment. Approximate estimates of  $RC_e$  can be made using the ratio of the dose to endosteal cells to the mean skeletal dose ( $D_e / D_s$ ) for radium of 7.5 ([Marshall et al. 1978](#)). [Puskin et al. \(1992\)](#) estimate a range of 7.5–9 for this ratio. Here we employ a central value of 8 for  $D_e / D_s$ .

There is a broad range of estimates in [Table 7-7](#), with values based upon exposures to  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ , to  $^{224}\text{Ra}$ , and to  $^{232}\text{Th}$  in Thorotrast. The possibility of no risk at low doses cannot be ruled out. Of the radium isotopes, the one most like plutonium in irradiation of the endosteal surfaces is  $^{224}\text{Ra}$ . Evidence on the induction of bone cancer, including that for  $^{224}\text{Ra}$ , favors a nonlinear dose-response model, such as the L-Q-E model of [Chmelevsky et al](#) (1986). For an average skeletal dose of 0.1 Gy, which exceeds doses likely to be encountered around Rocky Flats, the value of  $RC_e$  is  $\sim 1$  case per  $10^4$  P-Gy. The estimate of Mays (linear model) of 27 cases per  $10^4$  P-Gy is a clear upper bound for the  $^{224}\text{Ra}$  results in the dose range of interest. The range of estimates of  $RC_e$  based upon  $^{224}\text{Ra}$  is then 0–27 cases per  $10^4$  P-Gy. Application of the L-Q-E model by [Schlenker](#) (1982) to the  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$  data (radium dial painters) led to estimates of  $RC_e$  of 0–40 cases per  $10^4$  P-Gy, which is comparable to the range for  $^{224}\text{Ra}$ .

**Table 7-7. Summary of Risk Estimates for Bone Cancer**

Type and source of estimate	Bone cancer risk coefficient ( $RC_s$ or $RC_e$ ) (cases per $10^4$ P-Gy or per $10^6$ P-rad)	
	Skeleton ( $RC_s$ )	Endosteal cells ( $RC_e$ )
Radium ( $^{226}\text{Ra}$ , $^{228}\text{Ra}$ ) dial painters		
Threshold, <a href="#">Evans</a> (1974)	0 below $D_s = 10$ Gy	
Threshold, <a href="#">Thomas</a> (1994)	0 below $D_s = \sim 5$ Gy	
Linear, <a href="#">Mays and Lloyd</a> (1972)	46	
Dose rate, <a href="#">Raabe et al.</a> (1980)	0 below $D_s = 0.8$ Gy	
L-Q-E, <a href="#">Schlenker</a> (1982)		0–40
Patients treated with radium ( $^{224}\text{Ra}$ )		
Linear, <a href="#">Mays</a> (1982)		27
L-Q-E, <a href="#">Chmelevsky et al.</a> (1986)	100 at $D_s = 1$ Gy 8.5 at $D_s = 0.1$ Gy	
BEIR IV ( <a href="#">NAS/NRC</a> 1988)	200	
Patients receiving Thorotrast		
Linear, <a href="#">Mays and Spiess</a> (1979)	55–120	
Linear, BEIR IV ( <a href="#">NAS/NRC</a> 1988)	55–120 <sup>a</sup>	
Linear, <a href="#">Hunacek and Kathren</a> (1995)	20 <sup>a</sup> (9–50) <sup>b</sup>	
Ra and Pu, animals and humans		
Linear, <a href="#">DuMochel and Groër</a> (1989)	300 (80–1100) <sup>a,c,d</sup>	

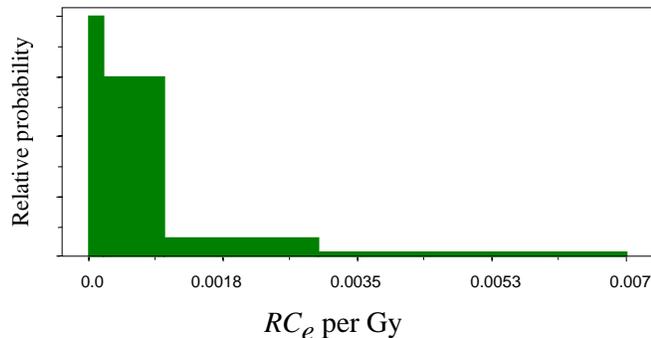
<sup>a</sup> Estimate stated to be “risk of death” per  $10^4$  P-Gy.  
<sup>b</sup> Weighted mean and range of values for the three cohorts for which estimates were made.  
<sup>c</sup> Median and 95% confidence interval for estimate.  
<sup>d</sup> These values, based primarily on animal data, have not been used in the estimate of human bone tumor risk.

The new estimates of risk for Thorotrast patients ([Hunacek and Kathren](#) 1995), with dosimetry based upon autopsy data, give values of  $RC_e$  of 1–6 cases per  $10^4$  P-Gy. Risk estimates based upon earlier dose estimates are higher, with a range for  $RC_e$  of 7–15 cases per  $10^4$  P-Gy.

Applying these results for radium and thorium to plutonium is not completely straightforward. The risk estimates for bone cancer produced by  $^{224}\text{Ra}$  are expected to be most

like those for plutonium and the range of possible values has been defined. However, choice of a central estimate remains problematic. The L-Q-E model results for  $^{224}\text{Ra}$  may not reliably predict the central risk estimate for plutonium.

Animal studies provide some information. From high-dose studies of mice designed to compare other radionuclides to  $^{226}\text{Ra}$  (Mays et al. 1989),  $^{239}\text{Pu}$  is estimated to be  $3.0 \pm 0.9$  times more effective in producing bone cancer than  $^{224}\text{Ra}$ . Lloyd et al. (1994) present toxicity ratios for bone cancer production by several radionuclides relative to  $^{226}\text{Ra}$ . These can be used to estimate that, in beagles, the effectiveness of  $^{239}\text{Pu}$  relative to  $^{224}\text{Ra}$  is  $2.0 \pm 0.9$ . An average effectiveness ratio of 2.5 is used. There were no comparisons that included  $^{232}\text{Th}$ .



**Figure 7-6.** Probability distribution for bone cancer risk ( $RC_e$ ) for  $^{239}\text{Pu}$

The probability distribution for the risk estimate  $RC_e$ , is shown in Figure 7-6 and summarized in Table 7-8. The range of the distribution is  $0\text{--}0.7 \times 10^{-2} \text{ Gy}^{-1}$ . The upper bound is based upon the animal results ( $0.27 \times 10^{-2} \text{ Gy}^{-1} \times 2.5$  effectiveness ratio). The 50<sup>th</sup> percentile is  $\sim 0.06 \times 10^{-2} \text{ Gy}^{-1}$ , and the 2.5 and 97.5 percentiles of the distribution are  $0.003 \times 10^{-2} \text{ Gy}^{-1}$  and  $0.49 \times 10^{-2} \text{ Gy}^{-1}$ , respectively.

**Table 7-8. Cumulative Probability Distribution for Bone Cancer Risk ( $RC_e$ ) for  $^{239}\text{Pu}$**

Value of $RC_e$ ( $\times 10^{-2} \text{ Gy}^{-1}$ )	Estimate of cumulative probability
0	0.0
0.02	0.2
0.1	0.8
0.3	0.95
0.7	1.0

#### 7.4 Risk Estimates for Leukemia

No firm evidence of excess leukemia was seen in dial painters exposed to alpha radiation from  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ . Ten cases were found in a population of 2940 workers, mainly female, while 9.2 were expected. The number of chronic lymphatic leukemia cases, which is not known to be radiation induced, (4 of the 10) in the group was also consistent with the expected number of 3.6 (Spiers et al. 1983). Nevertheless, Mole (1978) estimated a leukemia risk of 40 cases per

$10^4$  P-Gy (or per  $10^6$  P-rad) for the Thorotrast patients. The BEIR IV committee, using different dose estimates, gave a risk estimate of 50–60 leukemia cases per  $10^4$  P-Gy (or per  $10^6$  P-rad) ([NAS/NRC 1988](#)).

Estimates of leukemia risk depend upon both the diseases included in the category and the dosimetry estimates. In the Danish study of Thorotrast patients, the estimated risk of acute myelogenous leukemia with myelodysplasia is about 170 cases per  $10^4$  P-Gy. If chronic myelogenous leukemia, non-Hodgkins lymphoma, and multiple myeloma are included, the risk factor is about 250 cases per  $10^4$  P-Gy ([UNSCEAR 1994](#)).

[Hunacek and Kathren \(1995\)](#) analyzed the risk of leukemia in the German, Japanese, and Portuguese cohorts. They estimated fatal leukemia risks to be 330, 560, and 250 deaths per  $10^4$  P-Gy, for these cohorts, respectively. Their weighted mean value was 320 deaths per  $10^4$  P-Gy (or per  $10^6$  P-rad), even greater than that derived from the Danish study. Their estimates of bone marrow dose, based on analyses from a whole body autopsy, were in the range  $0.05$ – $0.08$  Gy  $y^{-1}$  per injection of 25 mL of Thorotrast. This estimate of  $0.08$  Gy  $y^{-1}$  is somewhat lower than the estimate of  $0.089$  Gy  $y^{-1}$  ([Kaul and Noffz 1978](#)) and their risk estimates are somewhat higher than reported previously for that group. However, the differences in dosimetry for the Japanese group are much greater,  $0.05$  Gy  $y^{-1}$  versus  $0.16$ – $0.37$  Gy  $y^{-1}$  reported previously by [Kato et al. \(1983\)](#). The dose estimates for Japanese cohort members were based upon samples collected from deceased cases. Lower doses were estimated for cases when the bone marrow was removed within a few days and estimates based upon later collections were considered suspect by [Kato et al. \(1983\)](#). An average bone marrow dose estimate that considers only the fresh samples is  $\sim 0.09$  Gy  $y^{-1}$ . This estimate was made by extracting information from a plot of values presented by [Kato et al. \(1983\)](#). Use of this approximate dose estimate would yield a risk estimate for the Japanese cohort,  $\sim 320$  deaths per  $10^4$  P-Gy, that is the same as the weighted mean estimate of [Hunacek and Kathren \(1995\)](#). The higher dose rates of [Kato et al. \(1983\)](#) are also quoted in BEIR IV ([NAS/NRC 1988](#)) and may have been used to derive the relatively low risk estimate of 50–60 deaths per  $10^4$  P-Gy cited above.

Our estimate of the risk coefficient for plutonium uses the central value from the Thorotrast experience but considers a broader range of uncertainty and the absence of leukemia in dial painters. The range of possible values is considered to be  $0.4 \times 10^{-2}$  Gy $^{-1}$  to  $8 \times 10^{-2}$  Gy $^{-1}$  and is described by a logtriangular distribution with a mode of  $3 \times 10^{-2}$  Gy $^{-1}$ . This yields a 50th percentile value of  $2 \times 10^{-2}$  Gy $^{-1}$ , the 2.5 and 97.5 percentiles of the distribution are  $0.6 \times 10^{-2}$  Gy $^{-1}$  and  $6 \times 10^{-2}$  Gy $^{-1}$ , respectively.

## 7.5 Summary

[Table 7-9](#) summarizes the estimates of risk per unit dose derived from studies of human exposures to alpha emitters other than plutonium. All of the estimates involve extrapolation from doses that are high when compared with those received by persons exposed to Rocky Flats releases or living in environmentally contaminated regions such as the offsite areas surrounding Rocky Flats.

These estimates of risk are not all the same. Those for lung cancer, liver cancer, and leukemia are risks of death. In contrast, the risk estimate for bone cancer is for incidence of the disease. In [Chapter 9](#), this bone cancer incidence risk distribution is converted to a mortality risk

distribution ([Table 9-1](#)) using data from Colorado ([Table 9-8](#)), before combining it with the mortality risk distributions determined using the other approaches.

Another difference among the estimates is the level of detail given for the lung cancer risks. This was feasible because of the extensive treatment of differences between smokers and nonsmokers and between genders in the BEIR VI report. The lung cancer risk estimates show the effects of smoking status on the risks posed by inhaled plutonium. Risk estimates for nonsmokers are more uncertain than those for smokers.

**Table 7-9. Distributions of Estimates of Risk ( $10^{-2}$  Gy $^{-1}$ ) of Cancer Based Upon Human Exposure to Alpha-Emitters Other than Plutonium**

Exposed tissue	Distribution type	Distribution parameters <sup>a</sup>	Resulting percentiles 50 (2.5, 97.5)
Lungs of smokers <sup>b,c,d</sup>			
Males	Lognormal	GM = 13; GSD = 2.8	13 (1.7, 98)
Females	Lognormal	GM = 3.3; GSD = 2.8	3.3 (0.44, 25)
Lungs of nonsmokers <sup>c,d</sup>			
Males	Lognormal	GM = 3.6; GSD = 3.9	3.6 (0.25, 52)
Females	Lognormal	GM = 1.5; GSD = 3.9	1.5 (0.10, 22)
Lungs of mixed population <sup>c,d</sup>			
	Lognormal	GM = 6.3; GSD = 2.6	6.3 (0.97, 41)
Liver <sup>d</sup>	Log-triangular	a = ln 0.5 b = ln 3 c = ln 15	3 (0.8, 10)
Endosteal cells of bone <sup>e</sup>	See <a href="#">Figure 7-6</a>	See <a href="#">Table 7-8</a>	0.06 (0.003, 0.49)
Bone marrow <sup>d</sup>	Log-triangular	a = 0.4 b = 3 c = 8	2 (0.6, 6)

<sup>a</sup> GM = geometric mean, GSD = geometric standard deviation, a = lower bound, b = most probable value (mode), c = upper bound, ln = natural logarithm.

<sup>b</sup> Category includes former and current smokers.

<sup>c</sup> Estimates are for persons living to age 75.

<sup>d</sup> Estimates are for risk of cancer death.

<sup>e</sup> Estimates are for risk of cancer incidence.



## 8. CONTROLLED STUDIES OF ANIMALS EXPOSED TO PLUTONIUM AND EXTRAPOLATION OF RISK ESTIMATES TO HUMANS

Data from studies of animals exposed to plutonium and other alpha-emitters support human risk assessment efforts in several ways ([Boecker et al. 1995](#)). Analyses of tissues of exposed animals provide information on the biokinetics of plutonium and on the changes in distribution within the body with time after exposure. Measurements of animal excretion of administered plutonium also provide data on the kinetics of plutonium retention and removal from the body. Data on the incidence of cancer and other effects in exposed animals can be a source of risk estimates for humans although there are problems inherent in such extrapolations. Results from animal studies are given lower weight in calculating our overall risk estimates because of the need to extrapolate those estimates to man (see [Chapter 9](#)).

One obvious difference between animals and humans is in life span, which is about 30 times longer for humans than for rats. Experimental animals may die a normal death before effects from plutonium exposure are expressed. Beagle dogs, which have been used in a number of studies of alpha- and beta-gamma-emitters, have a life span that is about 20% of the nominal human value of 70 years. Many of those studies have by now continued over the complete life span of the experimental animals. Analyses that account for competing risks of death in the animal life-span studies are discussed in later sections. Another problem is that the spectrum of tumor types and the number of each that may be induced in animals may be different from those induced in humans for example lung tumors induced in rats by radon may be of two broad types, fatal and incidental, with different dose responses and obviously different lethality ratios ([Heidenreich et al. 1999](#)).

A major advantage of animal studies is that they can be controlled. Known exposures of the isotope of interest are administered to groups of animals, usually over a range chosen to answer a particular question. Smoking, often a confounding factor in human studies, is not a concern in controlled animal studies. However, as with human studies, there are still uncertainties in the doses received by the tissues of interest. Methods of analysis of the data from animal experiments have improved over time. Presently, methods that are used in human epidemiological studies are often applied. A broad range of risk estimates is considered in this chapter. Some results were derived in the late 1970s, when methods were beginning to evolve. Others come from quite recent publications and are based upon state-of-the-art methods for analysis of dose-response data.

**Animal studies have the advantages that they can be carefully controlled and that smoking is not a concern.**

Two types of animal exposure studies are of particular interest. Included in the first category are those studies in which animals were exposed to plutonium and other radionuclides by inhalation, and the effects of the exposure were tracked. Other studies were designed to compare exposures to plutonium and other radionuclides with exposure to radium under the same experimental conditions. Injections were frequently used to administer the radionuclides in these experiments. The premise underlying these studies was that our knowledge of the consequences of radium exposure in man could be used to relate the results of comparative exposure experiments in animals to effects in humans.

Sections [8.1](#), [8.2](#), [8.3](#), and [8.4](#) discuss results of studies that have produced data on induction in animals of lung cancer, liver cancer, bone cancer, and leukemia, respectively. The discussion considers risk estimates made over a period of many years, from earliest ICRP evaluation of the

effects in lung ([ICRP 1980](#)) to a very recent analysis of two sets of life-span studies of beagle dogs ([Gilbert et al. 1998](#)). [Section 8.5](#) summarizes the results of the evaluation and presents estimates of risk for human populations that are based upon the animal data.

## **8.1 Lung Cancer Following Inhalation Exposures to Radioactive Aerosols**

This section examines results from experiments in which animals were exposed to radioactive aerosols by inhalation or bronchial intubation. Risks of lung cancer have been derived from the experimental data and comparisons of results for alpha-emitters with those from beta-gamma-emitters have provided estimates of the increased effectiveness of the alpha-emitters. A variety of different risk modeling approaches have been employed to analyze the data from animal experiments.

[Section 8.1.1](#) discusses the information in ICRP Publication 31 ([ICRP 1980](#)). Most of the pre-1980 information came from experiments with rodents. [Section 8.1.2](#) presents an approach for analysis of the animal data that considers average dose rate and time to death to be the most important variables. In [Section 8.1.3](#), we discuss results of an analysis that addresses a variety of time-related factors affecting age-specific risks from plutonium inhalation. The results of studies of plutonium inhalation by mice at Hanford are discussed in [Section 8.1.4](#), as is a comparison of the effects of radon progeny and plutonium in these animals. Sections [8.1.5](#) and [8.1.6](#) describe the plutonium inhalation studies at the Inhalation Toxicology Research Institute (ITRI). Results of the recent combined analysis of the effects of inhaled <sup>238</sup>Pu on Hanford and ITRI beagle dogs are presented in [Section 8.1.7](#). [Section 8.1.8](#) provides a summary.

### **8.1.1 ICRP Task Group Analysis of Early Animal Experiments to Derive Lung Cancer Risk Estimates**

A Task Group of Committee 1 of the ICRP performed an extensive review of the effects of inhaled radionuclides ([ICRP 1980](#)). The review had four main goals: (1) to list the biological responses following radionuclide deposition, (2) to identify tissues and cells at risk, (3) to derive risk coefficients from the data and compare them with ones obtained from human data, and (4) to determine the relative effectiveness of alpha-emitters compared to beta-gamma-emitters. The animal exposure data analyzed in their report, ICRP Publication 31, included some results for dogs, but most of the studies employed rodents ([ICRP 1980](#)).

The primary impacts on animal health noted were cancer induction; impairment of cellular defense mechanisms, particularly through lymphocyte damage; structural and functional changes in lung tissue, such as fibrosis of the lung; and life shortening ([ICRP 1980](#)). At lower dose levels, the principal effects were pulmonary tumors, pulmonary fibrosis and edema, and fibrosis of the tracheobronchial lymph nodes. At higher dose levels there was significant life shortening, primarily due to pulmonary fibrosis. It should be noted in this context that the experimental studies with soluble and insoluble alpha-emitters produced average lung doses that generally exceeded 0.1 Gy (10 rad) and were as high as 100 Gy (10,000 rad). The doses were often higher than thresholds for deterministic effects. It was observed that the peak tumor incidence for alpha-emitters occurred at doses of about 10 Gy (1000 rad). Use of risk coefficients derived from the animal data involves extrapolation from high to low doses as well as from animals to man.

The Task Group that prepared ICRP Publication 31 faced a major challenge in analyzing data from many laboratories to make estimates of lung cancer risks from inhaled radionuclides. There were, for example, differences in administration of the radionuclides and in the assessment of the doses that were received. Because some of the animals received very high doses, there were losses due to the competing risks of death noted above.

Estimates of cumulative dose to the lung presented in literature reports of the animal experiments were not always based upon the same periods of exposure. In some cases, the period of exposure was taken to be from inhalation until time of death or sacrifice; in others, the mean life span of the exposed animals was used. A better method of estimating lung doses is to rely upon experimental observation of the lung retention of the radionuclides. That approach was used in some studies but was not feasible in others. In all studies, doses were averaged over the entire lung.

The ICRP 31 Task Group developed criteria for including experimental studies in their evaluation of lung cancer risks from the animal data. It was assumed that malignancy ascertainment procedures were equally valid in all studies. If doses were reported in an unusual way or only as a broad range, the results of the study were not used. Experimental protocols that included multiple levels of dose were selected if a dose-response relationship was exhibited and if there was less than 30% shortening of animal lifespan. Experiments employing a single dose level were included if life span loss was less than 30% and if tumor incidence was consistent with results from multiple dose experiments.

The ICRP 31 Task Group analyzed the dose-response data in two ways. In one, they used the probit model, in which a nonlinear dose-response function with the shape of the cumulative normal distribution function, is fit to the dose-response data. Results from that approach were contrasted with those obtained using a linear dose-response model. The latter model is usually used to derive conservative risk estimates (estimates of risk that would be biased on the high side). These models were used for both data sets (results for alpha-emitters and for beta-gamma-emitters) although it was suggested that different models might be more appropriate. In the fitting procedure, points with larger binomial confidence intervals or fewer observations were given lower weights than results that were based upon many observations and had smaller confidence intervals. The ICRP 31 Task Group considered fits to the weighted data points for alpha-emitters to be adequate for both the linear and probit models. For the beta-gamma-emitters, they found that neither model provided a satisfactory fit to the incidence data, which were quite variable for similar doses. The linear model greatly overestimated incidence at low doses ([ICRP 1980](#)).

Estimates of cancer risk were derived from both linear and probit models and by using an improved Mantel-Bryan procedure ([Mantel et al. 1975](#)) available at the time. It was recognized that there were differences of opinion about the best way to extrapolate cancer risks at low doses ([ICRP 1980](#)). [Table 8-1](#) shows the results of these evaluations, expressed as lung cancer cases per  $10^4$  animal-Gy to lungs. The agreement between the Mantel-Bryan procedure and the probit model is not surprising because the two procedures are similar. The linear model estimate for all alpha-emitters was found to be in general agreement with an estimate for humans: 200–1200 cases of lung cancer per  $10^4$  P-Gy to lungs. That estimated risk range was largely based upon linear model analyses of cancer risks from external exposure to low-LET radiation and a quality factor of 20 ([ICRP 1980](#)).

In ICRP Publication 31, an equal effectiveness ratio for two radiations was taken to be the ratio ( $D_1 / D_2$ ) of the dose ( $D_1$ ) of radiation 1 required to produce an effect to the dose ( $D_2$ ) of

radiation 2 required to produce the same effect. This ratio is the same as the RBE as used in this report (see [Section 6.4](#)). The results of the Mantel-Bryan risk projection procedure presented in the second column of [Table 8-1](#) can be used to estimate equal effectiveness ratios for alpha-emitters as compared with beta-gamma-emitters. If both soluble and insoluble alpha-emitters are considered together, those results imply an alpha particle equal effectiveness ratio (RBE) of 30 (= 25 / 0.84) compared to beta-gamma radiation. The estimated equal effectiveness ratio for soluble alpha-emitters is 23 and that for the insoluble forms is 85.

**Table 8-1. Risk Estimates for Lung Cancer in Animals  
Based upon Rodent and Some Dog Data (ICRP 1980)**

Animals exposed to	Lung cancers per 10 <sup>4</sup> animal-Gy to the lung		
	Mantel-Bryan projection	Probit model	Linear model
Soluble alpha-emitters	19	20	a
Insoluble alpha-emitters	71	65	a
All alpha-emitters	25	36	360
Beta-gamma-emitters	0.84	a	a

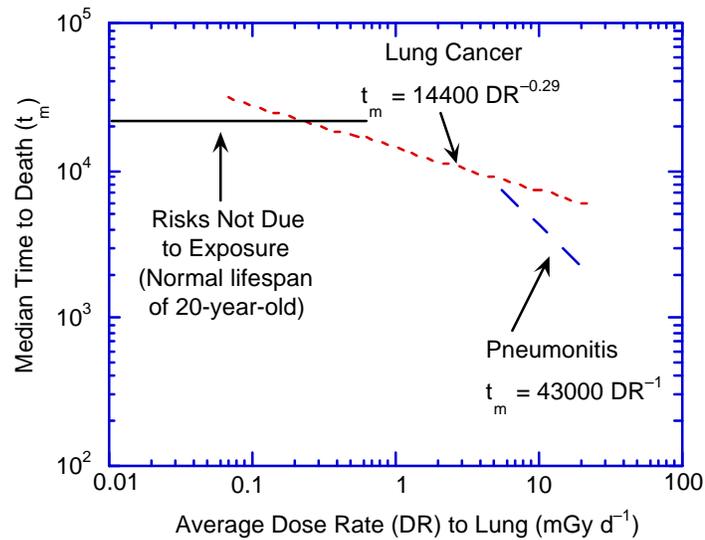
<sup>a</sup> No estimate made.

### 8.1.2 Analysis of Lung Cancer Risks from Plutonium Based upon Dose Rate and Time to Death

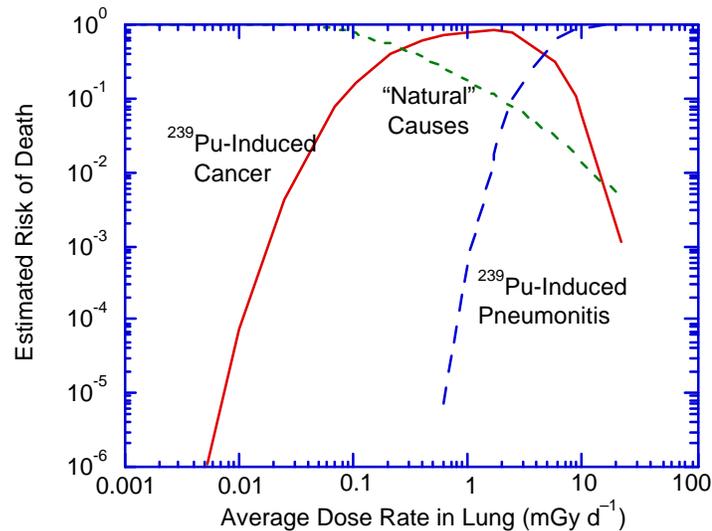
[Raabe](#) (1989) used a three-dimensional lognormal model relating risk to dose rate and time to death to analyze two sets of data on the effects resulting from plutonium dioxide inhalation by Beagle dogs and one set of data for rats. He considers that dose rate is the best exposure parameter to describe competing effects that result from inhalation of plutonium dioxide. The results for animal experiments have been extrapolated to estimate risks for human exposure. [Figure 8-1](#) illustrates the type of risk curves that are derived from his analysis in which median time to death is plotted against dose rate. There is not actually a unique dose rate because it decreases with time as plutonium is removed from the lung. Values of dose rate that were used by Raabe in the analysis and those shown in the plot were averaged over the period of exposure.

Three regions are evident in [Figure 8-1](#). At the highest dose rates, radiation pneumonitis/fibrosis is the cause of death, and the median survival time is inversely proportional to dose rate. At a dose rate of about 5 mGy d<sup>-1</sup> (0.5 rad d<sup>-1</sup>), risks of pneumonitis and lung cancer are comparable. Lung cancer is the dominant risk for intermediate dose rates. At a dose rate of 0.2–0.3 mGy d<sup>-1</sup> (0.02–0.03 rad d<sup>-1</sup>), the median lung cancer survival time is comparable to the expected life-span for a person exposed at age 20. For exposures producing lower dose rates to the lung, the principal causes of death are from “natural” causes not associated with the exposure to <sup>239</sup>PuO<sub>2</sub>, although cancer is included.

[Raabe](#) (1994) provided an updated analysis using the same general model. The result for lung cancer differs slightly from that shown in [Figure 8-1](#).



**Figure 8-1.** Estimated composite survival plot for humans exposed to airborne  $^{239}\text{Pu}$  based upon scaling of results from experiments with beagles and rats (scaled and redrawn from Raabe 1989).



**Figure 8-2.** Estimated risks of death in humans from  $^{239}\text{Pu}$ -induced lung cancer,  $^{239}\text{Pu}$ -induced pneumonitis, and “natural” causes unrelated to inhalation exposure to  $^{239}\text{Pu}$  (scaled from animal experiments using Raabe model).

An alternative way to view the results of this modeling approach is shown in Figure 8-2, which plots the estimated risks of death against dose rate. For an average lung dose rate of  $0.005 \text{ mGy d}^{-1}$  ( $0.0005 \text{ rad d}^{-1}$ ), which corresponds to a cumulative dose of  $0.1 \text{ Gy}$  ( $10 \text{ rad}$ ) over 55 years following exposure at age 20, the risk of death from  $^{239}\text{Pu}$ -induced lung cancer is estimated

to be  $10^{-6}$ . The lung cancer risk is estimated to increase rapidly with dose rate. At an average dose rate of  $0.011 \text{ mGy d}^{-1}$  to the lung from  $^{239}\text{Pu}$ , the risk of lung cancer is about  $10^{-4}$ . At even higher dose rates,  $^{239}\text{Pu}$ -induced lung cancer becomes the primary cause of death. At dose rates above about  $2 \text{ mGy d}^{-1}$ , lung cancer risk declines as deaths from gross lung damage increase and dominate.

In the model used by Raabe, the risk is not linearly proportional to the dose and the risk estimates differ substantially from those obtained from other models. To illustrate, we compare the doses that are predicted to produce a lifetime risk of  $10^{-6}$ . For the Raabe model, that is  $0.1 \text{ Gy}$  ( $10 \text{ rad}$ ) as indicated above. From [Table 8-1](#), we see that the Mantel-Bryan and probit analyses indicate that doses of  $0.14\text{--}0.16 \text{ mGy}$  ( $14\text{--}16 \text{ mrad}$ ) would produce that level of risk for insoluble alpha-emitters like the  $\text{PuO}_2$  exposures evaluated by Raabe. The Raabe model predicts that a lung dose of  $0.22 \text{ Gy}$  ( $22 \text{ rad}$ ) from insoluble  $^{239}\text{PuO}_2$  over 55 years would produce a risk of  $10^{-4}$ . For insoluble alpha-emitters, [Table 8-1](#) indicates that a dose of  $14\text{--}16 \text{ mGy}$  ( $1.4\text{--}1.6 \text{ rad}$ ) would produce a lung cancer risk of  $10^{-4}$ . The linear model for all alpha emitters predicts that a dose of  $2.8 \text{ mGy}$  ( $0.28 \text{ rad}$ ) would produce a lung cancer risk of  $10^{-4}$ . The other models for all alpha emitters predict that doses 10–14 times higher would be required to have the same effect.

A second major difference in the model used by Raabe is that it predicts that there is an average dose rate and cumulative dose below which there is no expression of lung cancer. [Evans](#) (1974) coined the term “practical threshold” to describe the dose below which no radium-induced bone cancers were observed in the cohort of dial painters (see [Section 7.3.2](#)).

### 8.1.3 Results for Lung Cancer from $^{238}\text{Pu}$ and $^{239}\text{Pu}$ Inhalation Experiments at Hanford Using Beagle Dogs

[Gilbert et al.](#) (1989a) used statistical methods that account for time-related factors such as age and follow-up to analyze the results of experiments involving inhalation of oxides of  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$  by groups of Beagle dogs at Hanford. Exposures corresponded to initial lung burdens ranging from 1 to 2800 times the permissible lung burdens for plutonium workers. With the exception of the highest dose group, which contained fewer dogs, there were 20 dogs in each dose group ([Park et al.](#) 1986). Total doses to the dogs’ lungs ranged from  $<1 \text{ Gy}$  ( $<100 \text{ rad}$ ) to  $50 \text{ Gy}$  ( $5000 \text{ rad}$ ). Follow-up was nearly complete—16 years for those exposed to  $^{239}\text{Pu}$  and 13 years for the groups exposed to  $^{238}\text{Pu}$ . The status of the studies was described by [Park et al.](#) (1986). Complete results for  $^{238}\text{Pu}$  have now been published ([Park et al.](#) 1997). Risk estimates based on that work are discussed below in [Section 8.1.7](#).

Two factors affected the distribution of doses to the dogs exposed to these two isotopes of plutonium. First, the specific activity ( $\text{Bq g}^{-1}$  or  $\text{nCi g}^{-1}$ ) of  $^{238}\text{Pu}$  is much greater than that of  $^{239}\text{Pu}$ . For  $\text{PuO}_2$  particles of a particular size, about 300 times fewer particles of  $^{238}\text{Pu}$  were needed to produce the desired lung burden. Second, there was a difference in retention of deposited particles in the lung. The  $^{238}\text{Pu}$  particles were cleared more rapidly because of particle fragmentation during radioactive decay, and more of the activity is subsequently deposited in the liver and skeleton. Cancers produced in these tissues are competing risks that can affect the analyses of the lung cancer outcomes. Also, as shown in [Figure 8-1](#), radiation pneumonitis is a competing risk for the animals exposed to high doses of  $^{239}\text{Pu}$ . Because of the slower clearance of  $^{239}\text{Pu}$  from the lung, the total dose from that nuclide is

<p><b>The specific activity of <math>^{238}\text{Pu}</math> is about 300 times greater than that of <math>^{239}\text{Pu}</math>.</b></p>
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delivered over a longer time period. In these experiments, about 80% of the dose from  $^{238}\text{Pu}$  was delivered in 3.4 years; however, the time required to deliver the same fraction of the dose from  $^{239}\text{Pu}$  was 7.3 years.

[Gilbert et al.](#) (1989a) found that there was a significant difference in lung tumor incidence between the two plutonium isotopes;  $^{238}\text{Pu}$  was less effective in producing lung tumors than  $^{239}\text{Pu}$ . The dose-response function was found to be nonlinear over the dose range of the experiments. A linear-quadratic dose-response model did not describe the data as well as a pure quadratic model. For each isotope ( $i$ ), the relative risk ( $RR_i$ ) was proportional to the square of the total dose ( $D_t$ , Gy), which was averaged over the whole lung. The best-fit equations for the relative risk functions for the two nuclides were

$$RR_{239} = 1 + 0.93D_t^2 \quad (8-1)$$

$$RR_{238} = 1 + 0.40D_t^2 \quad (8-2)$$

The different results for the two nuclides may be related to the distribution of dose in the lung. Because there are many more particles of  $^{239}\text{Pu}$ , the dose would likely be more widely distributed over the lung mass. [Muggenburg et al.](#) (1989) studied the effects of non-uniform radiation doses from  $^{239}\text{Pu}$  to the lungs of beagle dogs. They used particles of differing diameters to deliver comparable mean doses to the lungs. Fewer large particles gave a less uniform dose distribution than a greater number of small particles. Three physical diameters in the range 0.18–0.96  $\mu\text{m}$  were used. The range in numbers of particles needed to produce the same  $^{239}\text{PuO}_2$  activity was about 150. No differences in lung cancer production had been observed in dogs surviving 9–11 years following inhalation exposure. However, the difference (a factor of 300) in the numbers of  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$  particles of the same size in the Hanford studies exceeds the range studied by [Muggenburg et al.](#) (1989), so their partial result does not eliminate the hypothesis that  $^{239}\text{Pu}$  is more effective because the dose is more widely distributed over the lung tissue.

As discussed above, there were temporal as well as spatial differences in the dose distributions from the two isotopes. Whether the spatial differences or the protraction of the exposure period was most important is not known. However, the results suggest that a simple analysis using incidence and cumulative average dose is inadequate to analyze such experimental data.

#### **8.1.4 Results for Lung Cancer from $^{239}\text{PuO}_2$ Inhalation Experiments at Hanford and the Inhalation Toxicology Research Institute Using Rats**

Lung cancer produced in rats by plutonium dioxide has been another major research focus of the radiation biology group at the Hanford site. Life-span studies with rats have the advantage that many more animals can be used for exposures at various levels and for controls. In the largest Hanford life-span study, in which female Wistar rats were exposed to plutonium dioxide, more than 500 rats were used in each of the two lowest dose (0.04–0.07 Gy or 4–7 rad) groups and about 1050 rats were used as controls. Overall, there were about 3160 rats in exposed and control groups and nearly 800 more animals were used to check aspects of plutonium clearance and dosimetry ([Sanders et al.](#) 1993a). In a status report, [Sanders et al.](#) (1986) stated that the study

of lung cancer in rats exposed to  $^{239}\text{PuO}_2$  had the goal of detecting, with  $p < 0.05$ , a 1% increase in lung cancer above the background rate. At the start of the study, the background lung tumor incidence rate was expected to be ~0.1%. The rate for unexposed rats was later reported to be 0.6% (Sanders et al. 1988c).

Median sizes of the  $^{239}\text{PuO}_2$  particles that were administered were in the range 1.0–2.6  $\mu\text{m}$ ; GSDs of the size distributions were 2.0–2.5. The median particle size was larger for dogs who received higher doses, as indicated by the initial lung burden (ILB) of  $^{239}\text{PuO}_2$ .

An important aspect of the studies with rats at Hanford has been evaluation of the distribution of inhaled particles, and thus of dose, within the lungs of the exposed rats (Sanders 1972, 1975; Sanders et al. 1988a,b). Macrophages collect plutonium particles deposited in the alveolar region and are responsible for the initial clearance of material from this region. However, the clearance rate is reduced if the loading is high or there is simultaneous exposure to other particles (Sanders 1972, 1975). Aggregates of plutonium particles were observed to occur in regions of fibrosis that were produced by plutonium or other contaminants (Sanders 1972, 1975; Sanders et al. 1988a,b). Such aggregates of particles lead to high doses to small volumes of tissue and to localized inflammation and fibrosis. Such regions may be the principal sites of irradiation of bronchial or alveolar epithelial cells and of subsequent tumor development. However, aggregates of particles were not common on pleural surfaces and this was concluded to be the reason that small numbers of pleural mesotheliomas were observed in two life-span experiments in which rats had lung depositions of  $^{239}\text{PuO}_2$  (Sanders 1992).

In a study comparing residual particle distributions in the lungs of rats and hamsters, Rhoads et al. (1982) found that there were differences between the two species. The study was initiated because life-span studies of the two species had shown differences in tumor production, with many more tumors occurring in rats. In both species, accumulations of particles were found that resulted from translocation of particles that initially were more or less uniformly distributed in the alveolar region. Local distributions of particles in regions of the lung differed between species, with greater clustering of particles in rat lungs. Differences in the resulting dose distributions were considered a possible cause of the different tumor production in these two species (Rhoads et al. 1982).

Sanders et al. (1988c) prepared an interim report on the results of the large life-span study of rats exposed to  $^{239}\text{PuO}_2$  that was begun in 1982. All of the rats had died, but histopathological evaluations had not been completed for all rats. The shapes of the dose-response relationships for pulmonary fibrosis, incidence of abnormal cell types, and tumor incidence were similar. Significant differences between exposed and control animals occurred only at higher dose levels. Proportional hazards models were used to fit the lung tumor incidence data. It was found that a pure quadratic function provided the best description of the dose-response curve. A linear dose-response function did not fit the data over the entire dose range (0.04–55 Gy or 4–5500 rad) and addition of a linear component did not improve the fit achieved with a quadratic function alone. The best-fit function given by Sanders et al. (1988c) was  $RR = 1 + 0.0007352 x^2$ , where  $x$  was the average lung dose in rad. For doses of 10 and 100 rad (0.1 and 1 Gy) the relative risks of lung cancer are estimated to be 1.1 and 8.4, respectively. However, the dose estimates for the rats in this study have been revised (see below).

In the context of the multi-step theory of carcinogenesis, Sanders et al. (1988c) suggested that at low doses the initiation step (mutation) occurs but that tumors do not develop because the damage is repaired or is not expressed because the promotion step does not occur. They regarded

the steep quadratic increase in tumor expression as a result of promotion of malignant cell growth. Clustering of particles of  $^{239}\text{PuO}_2$  is believed to lead to high local doses and tissue inflammation, followed by fibrosis and metaplastic changes that ultimately result in lung tumors.

The quadratic dose-response reported for female Wistar rats by [Sanders et al.](#) (1988c) is not characteristic of all rats. [Sanders and Lundgren](#) (1995) have compared lung cancer production by  $^{239}\text{PuO}_2$  in female Wistar and female Fischer-344 (F344) rats. The latter species was studied at the Inhalation Toxicology Research Institute (ITRI), now known as the Lovelace Respiratory Research Institute. At low doses, lung clearance by the Wistar rats was faster than observed in the F344 rats. However, at high doses, clearance rates of plutonium from the lung were similar. Clearance functions were calculated for each rat individually because [Sanders et al.](#) (1993a) found clearance rates depended on dose (see below). Comparisons of lung tumor incidence were made for doses of  $\sim 1$  Gy ( $98 \pm 20$  rad for F344 and  $75 \pm 18$  rad for Wistar) and 35 Gy ( $3700 \pm 670$  rad for F344 and  $3400 \pm 730$  rad for Wistar). For the highest doses, estimated absolute risks of lung tumors were comparable,  $220 \pm 12$  and  $190 \pm 17$  cases per  $10^4$  rat-Gy to lungs of F344 and Wistar rats, respectively. At average lung doses of about 1 Gy, the absolute risk for Wistar rats was zero, compared to  $1900 \pm 550$  cases per  $10^4$  rat-Gy to lungs of F344 rats. Data from [Lundgren et al.](#) (1995) also show distinctly positive tumor incidence in the F344 rats at the  $\sim 1$  Gy average dose level. [Sanders](#) (1998) has since indicated that estimates of absolute risk for Long-Evans rats at the same dose levels are comparable to those for the F344 rats. That communication also indicated an estimated absolute risk of 90 cases per  $10^4$  rat-Gy to lungs of Wistar rats that received doses of 0.60–0.98 Gy (60–98 rad).

[Sanders et al.](#) (1993a) have presented a revised approach and new dose estimates for the female Wistar rats in the life-span study. The new approach reflects differences in clearance half-times in animals having different ILBs. Initial clearance, which removes about 80% of the  $^{239}\text{PuO}_2$  from rat lungs, was characterized by a half-time that was about 4 times greater for rats with an ILB of 3.9 kBq (0.11  $\mu\text{Ci}$ ) than the clearance half-time for rats with an ILB of 0.4 kBq (0.011  $\mu\text{Ci}$ ). The late clearance half-time for the higher ILB was 2–3 times greater than that for rats with ILB = 0.4 kBq. Individual lung dose estimates for exposed rats are based upon whole-body counting measurements of the gamma rays emitted by the ytterbium ( $^{169}\text{Yb}$ ) oxide tracer that is mixed with the administered  $^{239}\text{PuO}_2$ . Previously, plutonium retention in the lung had been estimated using the clearance function measured for rats with ILB  $\sim 0.4$  kBq. Corrected doses for animals in the higher exposure groups are higher than those estimated previously. For example, the highest average lung dose group is  $\sim 55$  Gy, compared with  $\sim 15$  Gy reported previously.

[Sanders et al.](#) (1993b) have used the revised average lung dose estimates in a preliminary analysis of survival and lung tumor incidence in the groups of female Wistar rats exposed to  $^{239}\text{PuO}_2$  at various dose levels. In general, the results are similar to those in the earlier paper [Sanders et al.](#) (1988c). No lung tumors were found in the groups with average lung doses of 0.056, 0.19, and 0.62 Gy, although the crude incidence of metaplastic changes was 1–3% in those groups. The crude incidence of lung tumors was about 7% in the next highest dose group (2.3 Gy). The incidence data suggest that the response function is complex (linear-quadratic or quadratic), rather than linear, and the author's believe that, in the female Wistar rat, there is an absolute threshold for lung cancer induction at  $>1$  Gy ([Sanders et al.](#) 1993b). Incidence data for the F344 rat species indicate a curvilinear response; as indicated above, that strain appears to be

more sensitive and exhibits a positive lung tumor response for average doses ~1 Gy ([Sanders and Lundgren 1995](#); [Lundgren et al. 1995](#)).

[Sanders et al. \(1993b\)](#) again emphasized the sequence of lung tissue inflammation, fibrosis, and metaplastic changes leading to lung tumors. The important role in that sequence of agglomeration of plutonium particles and higher local doses was also noted. Although not as common as obstructive lung disease (due to smoking), fibrosis (a restrictive lung disease) is a frequently observed pulmonary abnormality. [Lundgren et al. \(1991\)](#) found that pre-existing fibrosis of the lung did not lead to an increase in lung tumor production in rats exposed to  $^{239}\text{PuO}_2$ . In that study, lung fibrosis was induced with bleomycin about 6 weeks before exposure to  $^{239}\text{PuO}_2$  particles. Animals with fibrosis had shorter life spans than control animals, but lung tumor risks in animals with induced fibrosis followed by  $^{239}\text{PuO}_2$  were similar to those for animals exposed only to  $^{239}\text{PuO}_2$ . These results suggest that persons with uncomplicated pulmonary fibrosis due to other causes are probably not at greater risk of lung cancer from exposure to  $^{239}\text{PuO}_2$ . In an early study, [Sanders \(1975\)](#) found that exposure to both  $^{239}\text{PuO}_2$  and asbestos led to fewer lung tumors than exposure to  $^{239}\text{PuO}_2$  alone.

The final analysis of the data for female Wistar rats will consider models for age-specific lung cancer risk as a function of dose, similar to the analysis of the Beagle dog data ([Section 8.1.7](#)) by [Gilbert et al. \(1998\)](#). [Gilbert et al. \(1992\)](#) used that approach to compare lung cancer risks in male rats exposed to radon and in female rats exposed to  $^{239}\text{PuO}_2$  at Hanford. The experiments were not designed with this comparison in mind. However, pathological evaluations were considered to be comparable in the two studies. In their analysis of 230 rats exposed to  $^{239}\text{PuO}_2$  and 384 rats exposed to radon progeny, the hazard (age-specific cancer risk, which varies with age) was modeled as a function of dose accumulated over time. All groups of animals received average lung doses that exceeded 1 Gy. [Gilbert et al. \(1992\)](#) considered both exponential and linear-quadratic hazard functions. Whether lung tumors were fatal (the cause of death) or incidental (not the cause of death but discovered at autopsy) was also considered because that distinction affects calculations of the age-specific rates.

When all tumors were assumed to be incidental, a good fit to the data was provided by a power function of the dose and a linear-quadratic model provided a reasonable fit. A linear model could be rejected for that analysis. It was not possible to rule out an absolute risk model that took risk to be constant with age. The conversion factor between dose from  $^{239}\text{Pu}$  and radon progeny was estimated to be 5 mGy WLM<sup>-1</sup> for the power model and 4.9 mGy WLM<sup>-1</sup> for the linear-quadratic model. Both estimates are in the expected range ([Section 7.1.1](#)).

When all tumors were assumed to be fatal, it was not possible to find a common model form that adequately fit both sets of data. Good fits were found for a pure quadratic function for  $^{239}\text{Pu}$  and a linear function for radon progeny. A strong dependence of risk upon age was identified for this analysis. The largest difference between the risks from radon progeny and  $^{239}\text{Pu}$  was for average lung doses that exceeded 12 Gy. In the “low dose” region (<5 Gy) risks from the two types of exposure were comparable.

For animals that live to very old ages, it is difficult to tell whether a particular lung tumor was the cause of death. Because the sacrifice data for animals exposed to radon progeny were limited, it was not possible to determine statistically whether tumors are fatal or incidental. The most likely case is that there were some in both categories, but an analysis of the associated range of possibilities was not conducted ([Gilbert et al. 1992](#)).

[Gilbert et al.](#) (1992) found that tumor types differed in the two experiments, with more epidermoid/squamous carcinomas in rats exposed to  $^{239}\text{Pu}$  and more adenocarcinomas and adenomas in rats exposed to radon progeny. The risks for specific tumor types differed for the two types of radiation exposure; however, total tumor risks were comparable. When our understanding of the relationship between dose distribution and lung tumor production is greater, it may be possible to relate specific tumors to regional radiation doses.

### **8.1.5 Results for Lung Cancer from $^{238}\text{Pu}$ Inhalation Experiments at the Inhalation Toxicology Research Institute Using Beagle Dogs**

Studies of tumor induction following inhalation of particles of plutonium oxide have also been carried out at the Inhalation Toxicology Research Institute. The results of experiments with  $^{238}\text{Pu}$  are presented in detail by [Muggenburg et al.](#) (1996). Two aerosol sizes, with activity median aerodynamic diameters (AMADs) of 1.6 and 2.9  $\mu\text{m}$ , were used in the study. Twelve animals were exposed in each of six dose groups for each particle size. No significant differences in tissue distribution or excretion of the radionuclide were seen as a function of aerosol size and the data were grouped for analysis. There were 24 unexposed control dogs under the current protocol. These were augmented by 61 unexposed controls from earlier studies that were conducted in a very similar manner. There was no difference in survival between the two sets of control animals.

The overall range of lung doses was 0.16–68 Gy (16–6800 rad). Central dose estimates and ranges for the six dose groups were similar for the two aerosol particle sizes, but there was substantial overlap in the dose ranges. Doses were averaged over the entire lung and were computed for various times from exposure to death as required for the data analysis. Small amounts of  $^{169}\text{Yb}$ , a gamma-emitter, were incorporated into the inhaled particles and used to measure initial lung burdens and early retention in the lung. The initial lung burdens were also estimated using measurements of excreted  $^{238}\text{Pu}$  and the analysis of tissues obtained after the deaths of the animals ([Muggenburg et al.](#) 1996).

Radiation pneumonitis, lung cancer, bone cancer, and liver cancer were competing causes of death. All major organ systems were examined at autopsy in both exposed and control dogs. An unusually high incidence of tumors was not detected except in the three tissues noted above. This is consistent with expectations based upon the distribution of plutonium in the bodies of the dogs. There were no neoplasms related to bone marrow irradiation found although changes in the numbers of neutrophils in peripheral blood were observed. Pulmonary lymph nodes received relatively large doses but no tumors were found ([Muggenburg et al.](#) 1996).

Relative risks were estimated using a proportional hazards model that adjusted for competing risks by eliminating dogs from the analysis when they died without having contracted lung cancer. The 95% confidence interval for the estimated relative risk of lung cancer at doses between 1 and 4 Gy covered a range from  $\sim(\text{RR} / 3.3)$  to  $\sim(3.3 \text{ RR})$ . Most lung tumors were detected by annual radiography. Although it was somewhat uncertain, the estimated time between exposure and development of a lung tumor was shown to decrease as lung dose increased.

For dogs in the lower dose groups, with lung doses of 0.16 to  $\sim 5$  Gy (16 to  $\sim 500$  rad), the lifetime risk estimate derived for a dose of 1 Gy (100 rad) was 3300 lung cancer cases per  $10^4$  dog-Gy. No significant differences between male and female dogs were found. There was not a significant excess of lung cancer in the group of animals with lung doses between 0.16 and 1 Gy.

The reason for this observation was not clear and further analysis of the low-dose region was planned ([Muggenburg et al. 1996](#)).

### **8.1.6 Results for Lung Cancer from $^{239}\text{Pu}$ Inhalation Experiments at the Inhalation Toxicology Research Institute Using Beagle Dogs**

[Griffith et al. \(1992\)](#) investigated the importance of age at exposure to  $^{239}\text{Pu}$  dioxide aerosols. Two groups of Beagle dogs were exposed at ages 3 months (immature animals) and 13 months (young adults) to monodisperse particles of  $^{239}\text{PuO}_2$ . One hundred eight immature dogs were exposed to particles 1.5  $\mu\text{m}$  in diameter and groups of older dogs (252 in all) were exposed to aerosols with diameters of 0.75, 1.5, or 3.0  $\mu\text{m}$ . At the time of the report, the dogs exposed when immature had been followed 7–10 years and the dogs exposed as young adults had been followed for 11–13 years. No differences were seen in latency or in the lung carcinoma incidence rates. As in the study described in [Section 8.1.4](#), a proportional hazards model was used to analyze the data.

Initial lung burdens were estimated two ways: (1) using whole dog counting that relied on the  $^{169}\text{Yb}$  tracer incorporated into the inhaled particles and (2) using terminal burdens in body tissues and the results of measurements of plutonium in excreta over the lifetimes of the animals. The time dependence of the radiation dose was considered in calculating cumulative organ doses received prior to the time of this intermediate analysis or of death of the animal.

Analysis of all of the data for the  $^{239}\text{Pu}$  inhalation experiments at ITRI is still underway. Additional papers describing results for the young adult dogs are planned. Because the study that employed immature dogs was started later, the final results of those experiments will not be available until 1999 ([R.A. Guilmette 1998](#), Personal Communication).

### **8.1.7 Combined Analysis of the ITRI and Hanford Data on Lung Cancer in Beagle Dogs Following $^{238}\text{Pu}$ Inhalation**

[Gilbert et al. \(1998\)](#) have recently completed an analysis of lung cancer risks in 260 beagle dogs that inhaled  $^{238}\text{PuO}_2$  in the life-span experiments at Hanford and ITRI (see [Sections 8.1.3](#) and [8.1.5](#)). The age-specific risk of incidence of lung cancer was considered as a function of cumulative radiation dose received up to one year prior to death. Alternative lag periods for the dose estimates have little effect on the results for lung cancer because most of the dose is received within a few years after exposure. The age dependence of the risk was modeled using a Weibull function and different parameter values were allowed when fitting the Hanford and ITRI data. Several general forms of the dose-response relationship (linear, linear quadratic, power function, mixed function) were considered. The form that provided the best fit to the data was selected and the associated coefficients were determined.

Some differences were found in the experiments conducted at the two laboratories. The plutonium dioxide particles used at Hanford received more heat treatment than those used for dog exposures at ITRI. The Hanford  $\text{PuO}_2$  aerosol was retained in the dogs' lungs longer; consequently, the Hanford dogs received lung doses that were 2–3 times larger than those received by the ITRI dogs. Dosimetry methods were not identical, although both laboratories obtained autopsy tissue samples that provided a good definition of the organ and tissue burdens at death. That information was used together with excretion data obtained during the course of the experiments and with external counting data. However, both of the latter data sources have

larger uncertainties than are associated with analyses of plutonium in autopsy tissues. Based upon a comparison of an early method and the final approach used for the Hanford dogs, differences in the way the data were interpreted could affect doses by as much as 30%. Organ weights were considered to be constant fractions of the dog's total weight; thus the dose estimated for any individual dog was likely not the same as the true dose for that dog.

Estimates of risks from low doses (0.01 Gy or 1 rad) were based upon analysis of the data for dogs with lung doses that were less than 1 Gy (100 rad). The estimated lifetime risk of lung cancer obtained from a linear model was 2150 cases per  $10^4$  dog-Gy (or per  $10^6$  dog-rad) with a 95% confidence interval of 210–5000 cases per  $10^4$  dog-Gy. The central estimate is somewhat lower than that reported for the ITRI dogs alone (3300 cases per  $10^4$  dog-Gy, [Section 8.1.5](#)), but the confidence interval is quite broad and includes the earlier estimate.

### 8.1.8 Summary of Estimates for Lung Cancer

Lung cancer risk estimates from the animal studies are highly variable. This is due in part to differences in the amount of data available and in the methods of analysis. For exposure to plutonium dioxide, the risk estimates range from ~70 cases per  $10^4$  animal-Gy from the primarily rodent data reviewed in ICRP Publication 31 ([ICRP 1980](#)) to ~3300 cases per  $10^4$  dog-Gy (for a dose of 1 Gy) to the lungs of the ITRI dogs exposed to  $^{238}\text{Pu}$  ([Muggenburg et al. 1996](#)). Risk estimates for rats exposed to  $^{239}\text{PuO}_2$  lie in the same range. The recent combined analysis of the dog studies of plutonium yielded an estimate of 2150 cases per  $10^4$  dog-Gy, with a broad 95% confidence interval of 210–5000 cases per  $10^4$  dog-Gy. We believe that this analysis deserves greater weight because it covers a larger group than the ITRI data alone. In addition, there was greater rigor in the conduct of the later rat and dog studies and in the analysis of the results. In contrast, there were many difficulties associated with the initial ([ICRP 1980](#)) analysis of data from a broad range of experiments of differing quality.

The choice of models for analysis of the experimental data is clearly important and can lead to an order of magnitude difference in the estimated risks at high doses ([Table 8-1](#)). At low doses, the Raabe model suggests a “practical threshold” for expression of lung cancer in humans based upon animal data. No excess of lung cancer was seen in the lowest dose groups in the ITRI study, and further analysis of that range of exposure is underway. The quadratic functions for relative risks of  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$  that fit the Hanford dog data also predict small increases in the risk of lung cancer at low doses. The same is true for the female Wistar rat data, but that result is somewhat equivocal because of observed differences among rat species.

The results from the Hanford dog studies indicate that  $^{239}\text{Pu}$  is more effective than  $^{238}\text{Pu}$  in producing lung tumors. The ratio of relative risks ( $^{239}\text{Pu} / ^{238}\text{Pu}$ ) is about 1.4 at a dose of 1 Gy (100 rad) but only 1.005 at a dose of 0.1 Gy (10 rad).

Based upon the preliminary comparison between immature and young adult dogs exposed to  $^{239}\text{Pu}$ , age at exposure does not appear to be an important factor for lung cancer risk. Studies of Wistar rats exposed to  $^{239}\text{Pu}$  indicate higher risks for males than for females ([Sanders 1998](#)), a finding not seen in studies of humans.

We have used the result of the combined analysis for  $^{238}\text{Pu}$  as a guide, considered the uncertainty in that estimate, and considered a possible difference in risk between  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$ . For  $^{239}\text{Pu}$  we believe that a human lung cancer risk range from ~200 to 8,000 cases per  $10^4$  P-Gy (or per  $10^6$  P-rad) with a mode of 2,000 cases per  $10^4$  P-Gy (or per  $10^6$  P-rad) is appropriate. Because of the broad range of values, a log-triangular distribution is used to

represent the human lung cancer mortality risk coefficient distribution with a minimum value of  $2 \times 10^{-2} \text{ Gy}^{-1}$ , a maximum value of  $80 \times 10^{-2} \text{ Gy}^{-1}$ , and a mode of  $20 \times 10^{-2} \text{ Gy}^{-1}$ . From this distribution we can determine a 50th percentile value of  $16 \times 10^{-2} \text{ Gy}^{-1}$ . The 2.5 and 97.5 percentiles of the distribution are  $3 \times 10^{-2} \text{ Gy}^{-1}$  and  $56 \times 10^{-2} \text{ Gy}^{-1}$ , respectively.

## 8.2 Liver Cancer in Experimental Animals Following Exposures to Radionuclides

Estimates of liver cancer risks in animals have come from several studies with mice and dogs. In some studies, exposure was by inhalation; in other studies radionuclides were injected into the experimental animals. Rats that were exposed to high-fired plutonium dioxide did not exhibit liver cancer ([Sanders and Mahaffey 1979](#)). As with the lung and bone cancer results, not all the data analyses are complete and additional information will be forthcoming. Relevant research results are discussed below.

### 8.2.1 Results for Liver Cancer from $^{238}\text{Pu}$ Inhalation Experiments at the Inhalation Toxicology Research Institute Using Beagle Dogs

Details of this study have been described above in [Section 8.1.5](#). As noted there, particle fragmentation led to relatively rapid clearance of inhaled  $^{238}\text{Pu}$  dioxide from the lung and deposition in both bone and liver. Liver cancer was a late outcome in 20 animals exposed by inhalation to  $^{238}\text{Pu}$  dioxide. Liver cancer was a cause of death in only two animals, but 25 distinct tumors were found. The minimum time to clinical detection of a liver tumor was 1457 days, about 4 years.

**Clearance of plutonium from the lung is followed by uptake in other tissues.**

Results for animals in the lower dose groups were used to estimate the risks of liver cancer in dogs. For these animals, cumulative doses to the liver ranged from 0.15 to  $\sim 4.3 \text{ Gy}$  (15 to  $\sim 430 \text{ rad}$ ). For liver doses in the range 1–4 Gy, uncertainties in the estimated relative risk for liver cancer were comparable to those for lung cancer. Bounds on the 95% confidence interval ranged from about (RR / 3.3) to about (3.3 RR), which gives a range of about an order of magnitude. The lifetime risk for dogs receiving a dose of 1 Gy to the liver was estimated in this study to be 4200 liver cancers per  $10^4 \text{ dog}\cdot\text{Gy}$  (or per  $10^6 \text{ dog}\cdot\text{rad}$ ) for dogs with initial body burdens of  $< 3.3 \text{ kBq kg}^{-1}$ . Doses to the livers of dogs with those burdens of  $^{238}\text{Pu}$  would be  $\sim 4.3 \text{ Gy}$  or lower.

### 8.2.2 Results for Liver Cancer from Combined Analysis of Studies at Hanford and ITRI Using Beagle Dogs

[Gilbert et al.](#) (1998) have performed a combined analysis of data from studies at Hanford and ITRI in which beagle dogs were exposed to  $^{238}\text{PuO}_2$  by inhalation. [Section 8.1.6](#) contains information about the approach used and the results for lung cancer. The findings for liver cancer are discussed here.

There were 25 liver tumors in the two populations, with roughly two-thirds of them occurring in the ITRI dogs. Most (80%) of the liver tumors were considered to be incidental rather than fatal tumors. Liver tumor response was found to be linearly related to dose. Separate estimates of the slopes for the two sets of data were not statistically different, although the

estimate for the ITRI dogs was double that for the Hanford dogs. The combined analysis yielded risk coefficients that were statistically significant for all dogs with initial burdens less than 30 kBq kg<sup>-1</sup> and for dogs whose liver doses were less than 1 Gy.

[Gilbert et al.](#) (1998) estimated a broad 95% confidence interval of 800–7200 cases per 10<sup>4</sup> dog-Gy with a central value of 3300 cases per 10<sup>4</sup> dog-Gy (or per 10<sup>6</sup> dog-rad). The combined value for liver is somewhat less than the estimate for the ITRI dogs alone (4200 cases per 10<sup>4</sup> dog-Gy, see [Section 8.1.1](#)) and the confidence interval is narrower.

### 8.2.3 Results for Liver Cancer from <sup>239</sup>Pu, <sup>241</sup>Am, and Thorotrast Injection Experiments at the University of Utah Using Grasshopper Mice

[Taylor et al.](#) (1993) presented results of a study of liver cancer induction in the grasshopper mouse at the University of Utah. Groups of 20 mice were injected with <sup>239</sup>Pu citrate at two dose levels. A parallel group of 16 mice received similar injections and was used to determine the uptake, retention, and distribution of <sup>239</sup>Pu in the liver of this species. Data from the parallel study were used to estimate liver doses for the study animals. Average liver doses from <sup>239</sup>Pu were 8.64 and 16.2 Gy in the two groups.

Forty-five percent of the mice injected with <sup>239</sup>Pu developed liver tumors. In the higher dose group, all nine of the tumors were benign. In contrast, five of the nine tumors in the lower dose group were malignant. The fraction of tumors that were malignant was lower (0.28) in the mice exposed to <sup>239</sup>Pu than in previous experiments with <sup>241</sup>Am (0.58) and Thorotrast (0.88) in the same species. No tumors appeared in 49 control animals.

**Risks from Thorotrast appear to be due to the radioactivity, not the material itself.**

Results for the mice injected with <sup>239</sup>Pu were compared with groups of mice that received similar doses (8.57 and 15.6 Gy) from <sup>241</sup>Am injections in a previous experiment. The patterns of tumor development were described as similar ([Taylor et al.](#) 1993); however, the cumulative tumor incidences for <sup>239</sup>Pu in Figure 1 of that report are inconsistent with the data for that nuclide given in Table 1 of the same report. A dose-response function was derived using the results for <sup>241</sup>Am and Thorotrast (<sup>232</sup>Th) in which liver doses were less than 5 Gy. The <sup>239</sup>Pu results were not used in this procedure. [Taylor et al.](#) (1993) reported the following expressions for fractional incidence ( $p$ ) as a function of average dose to the liver ( $D$ , Gy):

$$p = (0.146 \pm 0.054) D \quad (\text{all tumors, } ^{241}\text{Am and } ^{232}\text{Th}) \quad (8-3)$$

$$p = (0.120 \pm 0.051) D \quad (\text{malignancies, } ^{241}\text{Am and } ^{232}\text{Th}) \quad (8-4)$$

Point estimates for risks from <sup>239</sup>Pu were reported as ~280 (150–500) cases per 10<sup>4</sup> mouse-Gy to liver at the highest dose level and ~520 (290–850) cases per 10<sup>4</sup> mouse-Gy to liver at the lower dose level.

Perhaps the main finding of the study was that results for Thorotrast, although more variable than those for <sup>241</sup>Am, appear to be attributable only to the radioactivity. This follows from the comparability of results for Thorotrast and <sup>241</sup>Am at doses <5 Gy and the stated similarity of the <sup>241</sup>Am and <sup>239</sup>Pu results at higher doses. This finding supports the use of the Thorotrast data in humans for other alpha-emitters; however, as noted above, there are differences in the fractions of tumors that were malignant.

### 8.2.4 Results for Liver Cancer from $^{239}\text{Pu}$ and $^{241}\text{Am}$ Injection Experiments at the University of Utah Using Beagle Dogs

Records of the occurrence of soft tissue tumors in beagle dogs have also been analyzed by [Lloyd et al.](#) (1995). Liver tumors, both malignant and benign, were the only soft tissue neoplasia whose rates of occurrence were significantly elevated in the exposed cohort. For both benign and malignant tumors, the rates calculated using the number of animals with tumors was not significant (at the 5% level), but it was significant (at the same level) if calculated using the number of benign or malignant primary tumors. The difference is due to the fact that some dogs were found to have multiple primary tumors of the liver. Tumors due to metastases from other sites were not considered to be primary tumors. A test for trend did not show a significant relationship for benign tumors, but significance was found for malignant tumors using the same test.

Broad dose groups were used in the analysis for trend. The numbers of malignant tumors found were: 4 among the 131 controls, 11 among the 179 dogs exposed to low levels ( $<1 \text{ kBq } ^{239}\text{Pu kg}^{-1}$ ), and 7 among the 57 dogs exposed to higher levels ( $>1 \text{ kBq } ^{239}\text{Pu kg}^{-1}$ ). The three proportions are 0.030 (0.01–0.07), 0.061 (0.03–0.11), and 0.12 (0.05–0.24), respectively. The indicated confidence intervals were estimated here based on the binomial distribution using information in [Burington and May](#) (1958). Because the slope of any best-fit line is highly dependent upon the location of the point with the highest incidence, the injection dose ranges are too broad to permit a reliable estimate of the risk factor for liver cancer in dogs.

A previous publication ([Taylor et al.](#) 1991) gives more detailed information about incidence for the various dose groups in the study and includes estimates of average doses to the liver and bone for each group. The numbers of animals exposed and the skeletal doses for the animals differ somewhat between [Taylor et al.](#) (1991) and [Lloyd et al.](#) (1993). New estimates of liver doses and the uncertainty in the dose estimates may be the subject of a future paper.

[Table 8-2](#) summarizes the data on liver cancer following injections of  $^{239}\text{Pu}$  and  $^{241}\text{Am}$  from [Taylor et al.](#) (1991). There is not a clear pattern of increasing risk with increasing dose to the liver for the animals receiving  $^{239}\text{Pu}$ . However, as noted above, the broad dose groups did show a trend. In the four lowest dose groups, for which bone cancer mortality was 22% or less, the liver cancer rates are not significantly different from the controls. The ITRI dog data showed liver cancer due to  $^{238}\text{Pu}$  occurred late in life and losses of life due to bone cancer induction may have precluded observation of liver cancer, particularly in the higher dose groups. Risks of liver cancer following injection of  $^{241}\text{Am}$  show a more distinctive pattern in the low dose groups and significant rates of liver cancer were seen even in the groups with high losses due to bone cancer.

**Table 8-2. Summary of Liver Doses and Tumor Experience for Utah Beagle Dogs Injected with  $^{239}\text{Pu}$  and  $^{241}\text{Am}$**

Average liver dose ( $D$ , Gy) <sup>a</sup>	Number ( $n$ ) of animals	Number ( $r$ ) with liver cancer	Fractional incidence ( $p = r / n$ )	Estimated 95% confidence interval for $p$ <sup>b</sup>	
				Lower	Upper
<u>Dogs receiving <math>^{239}\text{Pu}</math> citrate injections</u>					
0.04	28	0	0.0	0.0	0.11
0.09	45	5	0.11	0.04	0.27
0.27	37	0	0.0	0.0	0.09
0.51	35	3	0.086	0.02	0.25
0.76	25	3 <sup>c</sup>	0.12	0.034	0.30
1.76	13	4 <sup>d</sup>	0.31	0.11	0.59
3.07	12	1 <sup>d</sup>	0.083	0.004	0.35
5.44	12	1 <sup>d</sup>	0.083	0.004	0.35
11.5	12	0 <sup>d</sup>	0.0	0.0	0.24
24.9	9	1 <sup>d</sup>	0.11	0.0	0.29
<u>Dogs receiving <math>^{241}\text{Am}</math> citrate injections</u>					
0.12	14	0	0.0	0.0	0.21
0.39	14	4	0.29	0.10	0.61
1.06	19	13	0.68	0.43	0.85
2.89	23	11 <sup>c</sup>	0.48	0.25	0.68
5.02	12	5 <sup>d</sup>	0.42	0.18	0.71
8.93	13	2 <sup>d</sup>	0.15	0.028	0.43
18.3	12	4 <sup>d</sup>	0.33	0.12	0.65
59.1	3	0 <sup>d</sup>	0.0	0.0	0.63
<u>Unexposed control dogs</u>					
0	133	4	0.030	0.01	0.07

<sup>a</sup> Mean liver dose to a year before death from [Taylor et al.](#) (1991).

<sup>b</sup> From Table A-22 of [Natrella](#) (1963) or based on Table 14.57.1 of [Burington and May](#) (1958).

<sup>c</sup> Mortality due to bone cancer was about 40% in this group.

<sup>d</sup> Mortality due to bone cancer exceeded 70% in this group.

### 8.2.5 Summary for Liver Cancer Following Inhalation of $^{239}\text{Pu}$

Using the results of the combined analysis of the ITRI and Hanford data on  $^{238}\text{Pu}$  for dogs as a guide for  $^{239}\text{Pu}$ , we have estimated that human liver cancer risks could range from 500 to 10,000 cases per  $10^4$  P-Gy, with 3000 cases per  $10^4$  P-Gy (or per  $10^6$  P-rad) as the most probable value. This range overlaps the lower estimates from other animal experiments. A log-triangular distribution is used to represent the human liver risk coefficient distribution with a minimum value of  $5 \times 10^{-2} \text{ Gy}^{-1}$ , a maximum value of  $100 \times 10^{-2} \text{ Gy}^{-1}$ , and a mode of  $30 \times 10^{-2} \text{ Gy}^{-1}$ . From this distribution we can determine a 50th percentile value of  $26 \times 10^{-2} \text{ Gy}^{-1}$ . The 2.5 and 97.5 percentiles of the distribution are  $7 \times 10^{-2} \text{ Gy}^{-1}$  and  $74 \times 10^{-2} \text{ Gy}^{-1}$ , respectively. Experiments with mice indicate that liver cancer induction by Thorotrast is due to the radioactivity, not the colloidal material, and those experiments suggest lower risks of liver

cancer. Plutonium-239 and  $^{241}\text{Am}$  risks were similar at high dose levels in mice, but they were not similar over a range of doses to the livers of Beagle dogs.

The risk of liver cancer derived from the combined analysis of studies of  $^{238}\text{Pu}$  inhalation by Beagle dogs ([Gilbert et al. 1998](#)) appear to be about 10 times higher than those in humans exposed to Thorotrast. It is an open question whether the differences in risk estimates result from differences in radiosensitivity of the dogs, as is the case with bone cancer; differences in the distribution of the radionuclides in the liver; or some other factors.

### **8.3 Bone Cancer in Experimental Animals Following Exposures to Radionuclides**

Estimates of bone cancer risks in animals have come from several studies of varying design. Some exposures were due to translocation of plutonium to bone following inhalation exposure to  $\text{PuO}_2$  particles. In other experiments, radionuclides were injected into the animals. As with the lung and liver cancer studies, not all the data analyses are complete and additional information will be forthcoming. Relevant studies are discussed below.

#### **8.3.1 Results for Bone Cancer from $^{238}\text{Pu}$ Inhalation Experiments at ITRI Using Beagle Dogs**

In the ITRI study described in [Section 8.1.5](#), bone cancer was the most common outcome following inhalation of  $^{238}\text{Pu}$  dioxide. As noted in that section, particle fragmentation led to relatively rapid clearance of the activity from the lung and to deposition in both bone and liver.

As in the analysis of other cancers, results for animals in the lower dose groups were used to estimate the risks of bone cancer in dogs. For those animals cumulative doses to the skeleton ranged from 0.08 to ~1.8 Gy (8 to ~180 rad). Uncertainties in the estimated relative risk for bone cancer were large; bounds on the 95% confidence interval ranged from about (RR / 7.3) to about (7.3 RR) for skeletal doses less than 2 Gy. The lifetime bone cancer risk for dogs receiving a dose of 1 Gy to the skeleton was estimated in this study to be 7800 cases per  $10^4$  dog-Gy (or per  $10^6$  dog-rad).

#### **8.3.2 Results for Bone Cancer from $^{238}\text{Pu}$ and $^{90}\text{Sr}$ Inhalation Experiments at ITRI Using Beagle Dogs**

[Boecker et al. \(1995\)](#) describe a comparison of bone cancer induction in Beagle dogs that inhaled relatively soluble forms of  $^{238}\text{Pu}$  or  $^{90}\text{Sr}$ -Y at ITRI. Yttrium-90 ( $^{90}\text{Y}$ ) is produced by the decay of  $^{90}\text{Sr}$  and contributes to the radiation dose following intake of  $^{90}\text{Sr}$ . The data on bone cancer incidence were analyzed using proportional hazards modeling for both radiation types (alpha particles emitted by  $^{238}\text{Pu}$  and beta particles from  $^{90}\text{Sr}$ -Y). The ratio of doses to produce the same relative risks was used to measure the effectiveness of the two radiation types. They found  $^{238}\text{Pu}$  to be about 54 times more effective in producing bone cancers than  $^{90}\text{Sr}$ -Y when the comparison was based upon average skeletal dose. They estimated that if endosteal surface dose were used for comparison of  $^{238}\text{Pu}$  and  $^{90}\text{Sr}$ -Y, the effectiveness ratio would be about 5.

### 8.3.3 Results for Bone Cancer from $^{224}\text{Ra}$ Injection Experiments at Utah and ITRI Using Beagle Dogs

In a study initiated at the University of Utah and completed at ITRI, Beagle dogs (aged 20–22 months) were given single or multiple (10 or 50) weekly injections of a solution of  $^{224}\text{Ra}$  citrate ([Muggenburg et al. 1995](#)). The approach provided a comparison to humans that had received multiple injections of  $^{224}\text{Ra}$  to treat ankylosing spondylitis. Groups of 6–12 dogs were exposed at each of four dose levels for each injection protocol with six unexposed controls for each.

Mean skeletal doses to the exposed dogs ranged from 0.11–3.0 Gy (11–300 rad). Distribution and retention of the injected  $^{224}\text{Ra}$  were evaluated in a parallel study of  $^{224}\text{Ra}$  kinetics in six adult dogs. As noted in [Section 7.3.3](#),  $^{224}\text{Ra}$  is a short-lived radionuclide that decays while residing on bone surfaces. In contrast to  $^{226}\text{Ra}$ ,  $^{224}\text{Ra}$  deposition in bone produces a dose distribution more similar to that from the plutonium isotopes,  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$ .

Three dogs in the highest acute dose group succumbed to blood disease within three weeks after  $^{224}\text{Ra}$  injection and other dogs in the group exhibited decreased blood cell counts. Eighteen dogs developed 22 bone tumors, 17 of which were osteosarcomas. The data were analyzed using a proportional hazards model using time to tumor with correction for competing risks. Time to tumor was shorter (1610–2912 days) in dogs with the highest skeletal doses (2.5–3 Gy) than the time to tumor (1728–4762 days) in dogs with lower skeletal doses (0.1–1 Gy). There was a significant difference in time to tumor due to dose protraction in the highest dose group. The lifetime risks for dogs receiving 50 weekly injections were also greater (8400 cases per  $10^4$  dog-Gy to bone) than those in dogs receiving 10 weekly injections or a single injection (2000 and 2300 cases per  $10^4$  dog-Gy to bone, respectively). There was no statistical difference between the latter two risk estimates.

The risks for protracted injection of  $^{224}\text{Ra}$  are larger than those for injection of  $^{226}\text{Ra}$ . In the latter case, the dose is also protracted because of the much longer half-life of  $^{226}\text{Ra}$ , but much of the dose is delivered to mineral bone.

The estimated risks for bone cancer in dogs injected with  $^{224}\text{Ra}$  discussed above are substantially larger than those estimated for humans exposed to the same nuclide in the same manner. Those estimates range from 100 to 200 cases per  $10^4$  P-Gy to bone (see [Section 7.3.3](#)).

### 8.3.4 Results for Bone Cancer from $^{239}\text{Pu}$ and $^{226}\text{Ra}$ Injection Experiments at Utah Using Beagle Dogs

[Lloyd et al. \(1993\)](#) presented results of the Utah Beagle dog studies comparing the toxicity of  $^{239}\text{Pu}$  to that of  $^{226}\text{Ra}$ . The underlying strategy in these studies was to assess the ratio of the toxicity of a nuclide to that of  $^{226}\text{Ra}$  in the Beagle dog and to use that ratio together with the human experience with  $^{226}\text{Ra}$  to estimate the toxicity of the nuclide in humans. The radionuclides were injected into the experimental animals and a broad range of doses was used. Injection was chosen because the human  $^{226}\text{Ra}$  intakes were by ingestion or injection. The results have been expressed as toxicity ratios per unit absorbed dose, using  $^{226}\text{Ra}$  as the standard for comparison.

[Table 8-3](#) contains the experimental data for the 10 groups of dogs injected with  $^{239}\text{Pu}$  citrate and the 8 groups that received  $^{226}\text{Ra}$ . These data are examined in some detail because they illustrate some features that seem to be common to the history of bone cancer studies.

**Table 8-3. Summary of Skeletal Doses and Tumor Experience  
for Utah Beagle Dogs Injected with  $^{239}\text{Pu}$  or  $^{226}\text{Ra}$** 

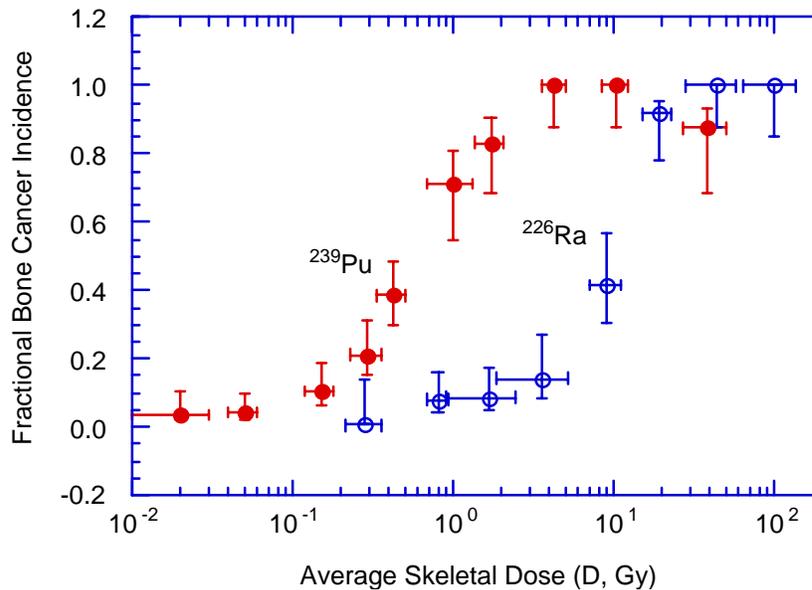
Average skeletal dose ( $D$ , Gy) <sup>a</sup>	Number ( $n$ ) of animals <sup>b</sup>	Number ( $r$ ) with bone cancer	Fractional incidence ( $p = r / n$ )	Estimated 95% confidence interval for $p^c$	
				Lower	Upper
<u>Dogs receiving <math>^{239}\text{Pu}</math> citrate injections</u>					
0.02 ± 0.01	28	1	0.036	0.002	0.17
0.05 ± 0.01	46	2	0.043	0.00	0.15
0.15 ± 0.3	38	4	0.11	0.03	0.27
0.29 ± 0.06	38	8	0.21	0.10	0.41
0.42 ± 0.09	26	10	0.38	0.21	0.58
0.99 ± 0.31	14	10	0.71	0.39	0.90
1.70 ± 0.32	12	10	0.83	0.55	0.97
4.26 ± 0.73	12	12	1.0	0.76	1.0
10.3 ± 1.9	12	12	1.0	0.76	1.0
38.4 ± 11.8	8	7	0.88	0.50	0.99
<u>Dogs receiving <math>^{226}\text{Ra}</math> injections</u>					
0.28 ± 0.07	10	0	0.00	0.00	0.27
0.80 ± 0.12	25	2	0.080	0.014	0.24
1.66 ± 0.77	23	2	0.087	0.016	0.26
3.57 ± 1.69	14	2	0.14	0.026	0.39
8.95 ± 1.98	12	5	0.42	0.18	0.71
19.1 ± 4.0	12	11	0.92	0.65	1.0
43.3 ± 15.1	12	12	1.0	0.76	1.0
101 ± 36	9	9	1.0	0.71	1.0
<u>Unexposed control dogs</u>					
0	132	1	0.0076	0.00	0.04

<sup>a</sup> Mean skeletal dose to a year before death, with standard deviation from [Lloyd et al.](#) (1993)

<sup>b</sup> Number that survived at least 2.79 y, the minimum observed latent period for bone cancer in the Utah Beagle dog colony.

<sup>c</sup> From Table A-22 of [Natrella](#) (1963) or based on Table 14.57.1 of [Burlington and May](#) (1958); in [Lloyd et al.](#) (1993) symmetric uncertainties for incidence are given, some of which include values of incidence that are less than zero or greater than one.

[Figure 8-3](#) is a plot of the bone cancer incidence for animals receiving either  $^{239}\text{Pu}$  or  $^{226}\text{Ra}$  as a function of the mean skeletal dose. The inception of the tumors was taken to occur a year before death and doses were estimated to that time. A logarithmic axis is used to show the results more clearly. The incidence of bone cancer in the lowest dose groups is not significantly different from controls (two groups for  $^{239}\text{Pu}$  and three groups for  $^{226}\text{Ra}$ ), but at higher doses there is a sharp increase in incidence. For  $^{239}\text{Pu}$ , nearly all dogs in the three highest dose groups contracted bone cancer and the lower incidence in the highest group may be due to cell killing. A similar picture is seen for  $^{226}\text{Ra}$ , with fractional incidences of 1 in the two highest dose groups.



**Figure 8-3.** Bone cancer incidence for  $^{239}\text{Pu}$  or  $^{226}\text{Ra}$  versus average skeletal dose for University of Utah beagle dogs. Skeletal dose was computed from injection to 1 year before death, the presumed time of tumor development.

[Lloyd et al.](#) (1993) describe the analysis of the  $^{226}\text{Ra}$  bone cancer incidence data, excluding the two highest dose groups, and represent it by a straight line:

$$p = 0.0076 + 0.047 D \quad (\text{for } ^{226}\text{Ra}, \text{Lloyd et al. 1993}) \quad (8-5)$$

in which  $p$  is the fractional incidence,  $D$  is the average skeletal dose (Gy), and 0.0076 is the tumor incidence in the control animals. For  $^{239}\text{Pu}$ , the same baseline incidence is used and the  $^{239}\text{Pu}$  bone cancer incidence data are represented by the following straight line

$$p = 0.0076 + 0.75 D \quad (\text{for } ^{239}\text{Pu}, \text{Lloyd et al. 1993}) \quad (8-6)$$

[Lloyd et al.](#) (1993) note that the equation is only valid for doses below about 1.3 Gy; thus, it cannot include the result for the group of dogs with  $D = 1.7$  Gy and  $p = 0.83$ . The ratio of the slopes of the two lines was used to derive a toxicity ratio for  $^{239}\text{Pu}$  citrate compared to  $^{226}\text{Ra}$ . Estimated uncertainties in the slopes were  $0.75 \pm 0.225$  for  $^{239}\text{Pu}$  and  $0.047 \pm 0.0047$  for  $^{226}\text{Ra}$  and the toxicity ratio of  $16 \pm 5$  was reported ([Lloyd et al.](#) 1993).

To evaluate the effect of not including all the data for doses below those that produced uniform incidence, we used a least squares fitting routine ([Meyer](#) 1975) that considered uncertainties in the incidence data. Approximate standard deviations were derived from the 95% confidence intervals for the fractional incidences in [Table 8-3](#). When the results for the controls and groups with doses below 2 Gy were included, the following best-fit equation was

$$p = (0.011 \pm 0.009) + (0.556 \pm 0.054) D \quad (\text{for } ^{239}\text{Pu}, \text{this report}) \quad (8-7)$$

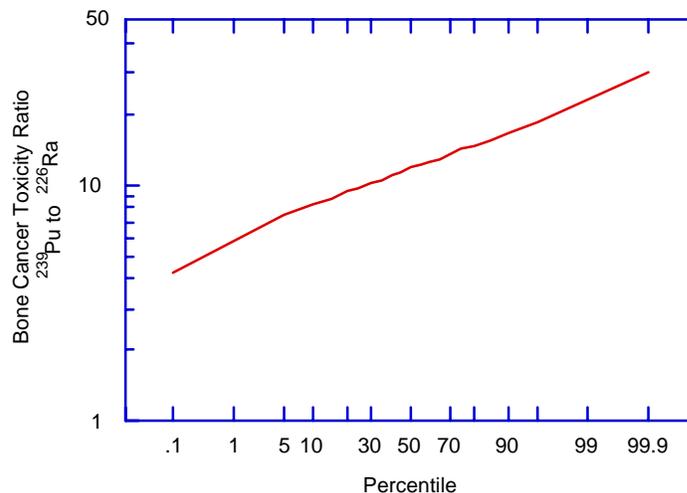
The estimated slope and its uncertainty are both lower than those estimated by [Lloyd et al. \(1993\)](#). The intercept, which does not differ significantly from zero, is also different because it was derived from the fitting procedure.

The data for  $^{226}\text{Ra}$ , excluding the two highest dose groups (with  $p = 1$ ), were fit using the same procedure. The best-fit equation was

$$p = (0.0095 \pm 0.0096) + (0.381 \pm 0.043) D \quad (\text{for } ^{226}\text{Ra, this report}) \quad (8-8)$$

The parameters of the best-fit line for  $^{226}\text{Ra}$  are also different from those cited above. The differences appear to be due to the fact that [Lloyd et al. \(1993\)](#) did not consider the uncertainties in the doses or incidence rates, took the intercept to be fixed, and adjusted the slope to yield the number of dogs with tumors.

We next performed a Monte Carlo analysis that considered both the uncertainties in the doses shown in [Table 8-3](#) and the uncertainties in the incidence values. Best-fit parameters for linear equations relating incidence to dose for both  $^{239}\text{Pu}$  with  $^{226}\text{Ra}$  were computed repeatedly and an estimate of the toxicity ratio was computed for each pair of estimated slopes. This procedure produced a distribution of toxicity ratios for  $^{239}\text{Pu}$  citrate injection compared to  $^{226}\text{Ra}$  injection. The distribution, shown in Figure 8-4, was approximately lognormal with a median of 11.7 and a GSD of 1.33.



**Figure 8-4.** Cumulative distribution of estimates of the  $^{239}\text{Pu}$  to  $^{226}\text{Ra}$  toxicity ratio based upon the Utah Beagle dogs. Calculations include uncertainties in average skeletal dose and tumor incidence ([Table 8-3](#)).

[Mays et al. \(1986\)](#) give other estimates of the  $^{239}\text{Pu}$  to  $^{226}\text{Ra}$  toxicity ratio for injection that range from  $6 \pm 3$  for male mice to  $22 \pm 7$  for female mice. No sex differences were observed in beagle dogs or in St. Bernard dogs for which a ratio of 7 has been estimated. These toxicity ratios are also based upon average dose to the skeleton.

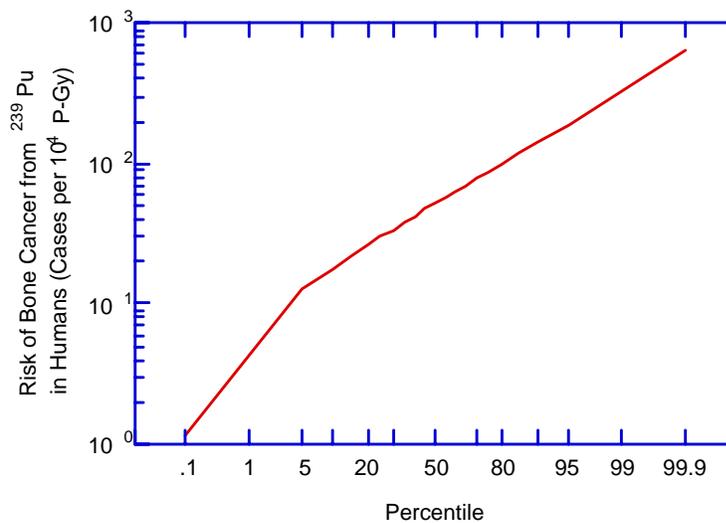
As discussed in previous sections of this report, direct comparison of  $^{239}\text{Pu}$  with  $^{226}\text{Ra}$  on an average skeletal dose basis is not appropriate. Plutonium deposits preferentially on bone surfaces and delivers more dose to the nearby endosteal cells, which appear to be most at risk for bone cancer. It has been estimated that, in humans, the dose to endosteal cells is 7.5 to 9 times greater than that to the skeleton as whole (Marshall et al. 1978; Puskin et al. 1992). In the case of  $^{238}\text{Pu}$  in Beagle dogs, we estimated a difference between the dose to endosteal cells and the mean skeletal dose of about a factor of 10 (see Section 8.3.2). These differences must be considered to estimate the risk of cancer induction for  $^{239}\text{Pu}$  on the basis of dose delivered to the critical tissues.

A gradual transfer of plutonium to the bone, such as the relatively slow removal from lung observed for  $^{239}\text{Pu}$ , is expected to be more effective in producing bone cancers than injections of plutonium citrate. On the basis of experiments with a few dogs, Lloyd et al. (1993), citing Bruenger et al. (1991), estimated that protracted transfer from an extra-skeletal deposit is a minimum of twice as effective for bone tumor production as intravenous injection. The data for  $^{224}\text{Ra}$  injections in Beagle dogs (Section 8.2.3) indicate an effect of protraction of about a factor of 4.

Risk estimates for  $^{226}\text{Ra}$ -induced bone cancer in humans given in NCRP Report No. 110 (NCRP 1991a) for a linear model range from 9 to 12 cases per  $10^4$  P-Gy. A nominal value of 10 bone sarcomas per  $10^4$  P-Gy is employed, with uncertainty bounds of 0 to 42 bone cancers per  $10^4$  P-Gy (NCRP 1991a). This estimate is taken as the starting point for an estimate of  $^{239}\text{Pu}$ -induced bone cancer following inhalation and gradual transfer of the plutonium to bone. The distribution of risks from  $^{226}\text{Ra}$  was taken to be triangular, with bounds of 0 and 42 and a mode of 10 bone sarcomas per  $10^4$  P-Gy. The distribution of the toxicity ratio for  $^{239}\text{Pu}$  compared to  $^{226}\text{Ra}$  was that shown in Figure 8-4. The factor to account for dose protraction due to gradual transfer to the bone was also considered to be a triangular distribution with a minimum of 2, a mode of 4, and a maximum of 8. The ratio of the dose to endosteal cells to the mean skeletal dose was taken to be a uniform distribution with bounds of 8 and 12. These factors were all combined using a Monte Carlo procedure to estimate the bone cancer risk for  $^{239}\text{Pu}$  in humans. Figure 8-5 shows the results of the Monte Carlo calculations. Except for the lower tail, the distribution is approximately lognormal. The median risk estimate for  $^{239}\text{Pu}$ -induced bone cancer in humans is 52 cases per  $10^4$  P-Gy, about 5 times greater than the risk for  $^{226}\text{Ra}$ . The GSD of the distribution is about 2.3. The 5th and 95th percentile values of the distribution are 13 and 190 cases per  $10^4$  P-Gy, respectively.

The result shown in Figure 8-5 may be compared with that of Raabe (1984). He used his three-dimensional lognormal model (see Section 8.1.2) relating risk to dose rate and time to death to analyze data from animal experiments to derive estimates of the relative effectiveness for various radionuclides compared to  $^{226}\text{Ra}$ . The estimates of relative effectiveness were 15 for  $^{238}\text{Pu}$  and 9 for  $^{239}\text{Pu}$ . The value of 9 for  $^{239}\text{Pu}$  lies within the range of estimates given above.

The bone deposition for  $^{239}\text{Pu}$  was due to injection of plutonium citrate; in contrast, the  $^{238}\text{Pu}$  entered the animals by inhalation. Therefore, the history of spatial distribution of the two nuclides in bone probably differed. Entry into the skeleton was more gradual for the  $^{238}\text{Pu}$ . The specific activity difference between these isotopes was discussed in Section 8.1.3. Using his earlier estimate of an 80-rad effective threshold for human bone cancer from  $^{226}\text{Ra}$ , Raabe (1984) estimated effective thresholds for bone cancer induction of 0.05 and 0.09 Gy (5 and 9 rad) for  $^{238}\text{Pu}$  and  $^{239}\text{Pu}$ , respectively.



**Figure 8-5.** Cumulative distribution of estimates of the risk of  $^{239}\text{Pu}$ -induced bone cancer per unit dose to endosteal cells in humans. The estimates were derived from the risk estimate for  $^{226}\text{Ra}$  using the  $^{239}\text{Pu}$  to  $^{226}\text{Ra}$  toxicity ratio in [Figure 8-4](#), with consideration of protraction enhancement effects.

### 8.3.5 Summary for Bone Cancer Following Inhalation of $^{239}\text{Pu}$

Risk estimates for bone cancer derived from the Beagle dog studies using  $^{238}\text{Pu}$  and  $^{224}\text{Ra}$  are substantially greater than estimates for bone cancer due to  $^{224}\text{Ra}$  injections in humans. Wide differences in bone cancer sensitivity among species have been noted before. [Mays et al.](#) (1986) recommended the use of a toxicity ratio based on comparisons with  $^{226}\text{Ra}$  as a more stable estimator of human risks. That recommendation has been followed in this report. We have used the toxicity ratio derived in [Section 8.3.4](#) to estimate the human bone cancer risk. The median estimate is 52 cases per  $10^4$  P-Gy. The distribution of estimates can be considered approximately lognormal with a GSD of 2.3.

### 8.4 Leukemia in Experimental Animals Following Exposures to Radionuclides

Induction of leukemia has not been a common finding in the experimental studies of animals discussed in this chapter. A figure in the paper by [Hahn et al.](#) (1996) indicates that one leukemia was observed in the 41 dogs that received inhalation exposures to  $^{144}\text{Ce-Pr}$ , a beta-gamma-emitter. No leukemias were identified in the reports of the ITRI studies of Beagle dogs exposed to  $^{238}\text{Pu}$  ([Muggenburg et al.](#) 1996) or to  $^{224}\text{Ra}$  ([Muggenburg et al.](#) 1995).

In the Utah studies of Beagle dogs injected with  $^{239}\text{Pu}$ , two leukemias were found in the 236 exposed dogs, compared with a single leukemia in 131 control animals. A myeloid sarcoma was also found in one of the exposed dogs. There was no significant difference in the rates of hematopoietic cancers and the authors concluded that it was unlikely that leukemias would be a consequence of entry of  $^{239}\text{Pu}$  into the blood ([Lloyd et al.](#) 1995).

Based on the available animal studies, there is no significant excess risk of leukemia from plutonium exposure. Approximate upper bounds to the leukemia risk can be estimated from the ITRI  $^{238}\text{Pu}$  study and the Utah  $^{239}\text{Pu}$  study. In making these estimates it was assumed that the alpha particle dose to bone surfaces was 10 times that to the whole skeleton and that the alpha particle dose received by bone surfaces was 20 times that received by bone marrow. In the ITRI study, the total dose to the skeletons of the 144 dogs was about 321 Gy and the dose to the bone marrow of those dogs is estimated to be about 160 Gy. There were more (234) dogs exposed in the Utah study; the total skeletal dose was about 547 Gy. The dose to the bone marrow was estimated to be about 270 Gy. Taken separately, the ITRI and Utah studies lead to estimated upper bound risks of leukemia of <62 cases per  $10^4$  dog-Gy and <37 cases per  $10^4$  dog-Gy, respectively. If the results are pooled, we obtain an upper bound risk estimate for leukemia of <23 cases per  $10^4$  dog-Gy. Based on this, the range of possible values of the human risk is assumed to be 0–23 cases per  $10^4$  P-Gy. A uniform distribution that ranges from 0 to  $0.3 \times 10^{-2}$   $\text{Gy}^{-1}$  is used to represent the human risk coefficient.

## 8.5 Summary

Table 8-4 summarizes the risk estimates developed in this chapter. In addition to the central estimates of cancer risk, the table shows the bounds for those estimates and the type of distribution chosen to represent them. In all cases, the risk estimates are for cancer incidence. Before combining them with the other risk estimates from Chapters 5–7 to determine an overall risk estimate, they will be converted to equivalent human mortality risk estimates (see Section 9.1). The conversion is made using human data from Colorado (Table 9-8) even though it is recognized that many animal tumors may have very different lethality fractions from those of humans. Therefore, additional uncertainty arises in the risk estimates derived from animals for this reason alone.

**Table 8-4. Cancer Incidence Risk Estimate Distributions ( $10^{-2}$   $\text{Gy}^{-1}$ )  
Based Upon Studies of Animals Exposed to Plutonium**

Exposed tissue	Distribution type	Distribution parameters <sup>a</sup>	Resulting percentiles 50 (2.5, 97.5)
Lung	Log-triangular	a = ln 2 b = ln 20 c = ln 80	16 (3, 56)
Liver	Log-triangular	a = ln 5 b = ln 30 c = ln 100	26 (7, 75)
Bone	Lognormal	GM = 0.52 GSD = 2.5	0.52 (0.09, 3)
Bone marrow	Uniform	a = 0 c = 0.3	0.15 (0.008, 0.3)

<sup>a</sup> a = lower bound, b = most probable value (mode), c = upper bound, ln = natural logarithm, GM = geometric mean, GSD = geometric standard deviation.



## 9. OVERALL ESTIMATES OF LIFETIME CANCER RISK COEFFICIENT DISTRIBUTIONS

In this chapter the results of the four different approaches are combined to derive an overall lifetime risk of fatal cancer for the four cancer sites of interest. The method that is used to combine the different distributions resulting from each approach is based on assigning a score for the intrinsic merit of each approach. The method is explained in [Section 9.1](#) and the resulting population-averaged lifetime mortality risk coefficients are presented in [Section 9.2](#). Some comparisons of this method with other methods for deriving the risk coefficients are described in [Section 9.3](#). These comparisons include

- Solicitation of expert opinion on the scores of intrinsic merit
- Comparison with assigning each approach an equal weight, and
- Comparison with risk estimates that might have been determined from other available information.

In [Section 9.4](#), Colorado data on 20-year cancer survival rates are used to provide lethality fractions with uncertainties, for each cancer site. These are applied to the mortality risk estimates to derive comparable incidence risk estimates. The total lifetime cancer incidence risk from exposure to plutonium via inhalation is also estimated. In [Section 9.5](#), the impact of age at exposure and gender on the risk coefficients is discussed and in [Section 9.6](#) final estimates of risk coefficients per unit dose are presented which take into account all the foregoing. Risk coefficients are also presented per unit intake of activity from aerosols with AMADs of 1  $\mu\text{m}$ , 5  $\mu\text{m}$ , and 10  $\mu\text{m}$ . Detailed accounting of the percentiles of all the distributions calculated in this chapter is provided in [Appendix A](#).

### 9.1 Method of Combining Independent Estimates of Risk

The risk estimates determined for each cancer site using the different independent approaches described in Chapters [5](#), [6](#), [7](#) and [8](#) are summarized below in [Table 9-1](#). Because of data limitations, not all approaches yield a risk estimate; for example, the epidemiology studies with plutonium yield a risk estimate for the lung only. The objective of this study is to determine an overall estimate of the risk with uncertainty for each cancer site based on all appropriate approaches. To accomplish this it was necessary to convert the risks of cancer incidence to risks of cancer mortality. All the risk estimates listed in [Table 9-1](#) were placed on a common basis, i.e., mortality, in preparation for deriving the overall risk estimates.

The uncertainty associated with each risk estimate reflects the uncertainties identified in the approach, but does not take into account a more intangible but very real factor, namely the intrinsic merit of the approach for the purposes of this task. Because the four approaches are not considered equally well suited to estimating plutonium risk, a method of scoring the intrinsic merit of each approach to weight each risk estimate was considered necessary. Included in what is meant by intrinsic merit is the degree of directness of the approach and therefore the reliance on fewer factors, whether more or less certain, to estimate the risk. In this respect the four approaches are certainly not equal and differ in a variety of aspects, only some of which are accounted for by the assigned uncertainties.

An alternative method is to assign a weight that combines both the intrinsic merit and the uncertainty in the estimate. We chose not to adopt this method because it is very sensitive to the relative magnitudes of the uncertainties and the shapes of the distributions. Every effort was

made to identify and account for the uncertainties in a given approach but it was not possible to account for them in an entirely consistent manner.

**Table 9-1. Summary of Distributions of Lifetime Cancer Mortality Risk Estimates ( $10^{-2}$  Gy $^{-1}$ ) by Cancer Site for the Different Risk Estimation Approaches<sup>a</sup>**

Cancer site	Epidemiology with plutonium	Low-LET risk estimate with RBE factor	Human exposures to other alpha-emitters	Controlled studies of animals
Lung	20 (5–80)	11 (2–76)	6 (1–41)	15 <sup>c</sup> (3–53)
Liver	–	8 (1–58)	3 (0.7–10)	25 <sup>c</sup> (7–72)
Bone <sup>b</sup>	–	0.6 (0.04–9)	0.03 <sup>c</sup> (0.001–0.2)	0.3 <sup>c</sup> (0.04–2)
Bone marrow (leukemia)	–	1.2 (0.2–6)	2 (0.6–6)	0.11 <sup>c</sup> (0.007–0.2)

<sup>a</sup> 50th percentile of distribution is shown with 2.5 and 97.5 percentiles in parentheses.

<sup>b</sup> Based on dose to endosteal cells.

<sup>c</sup> Estimates that reflect cancer incidence have been converted to mortality estimates using lethality data presented in [Table 9-8](#).

In this report we have assessed the intrinsic merit of each approach by scoring on a 10-point scale. A score ( $s_j$ ) of 10 would indicate that the approach is considered ideally suited for estimating plutonium risk in humans. In the following subsections the intrinsic merit of each approach is discussed and a score assigned. The scores are summarized at the end of this section in [Table 9-2](#).

### 9.1.1 Intrinsic Merit of Epidemiologic Studies of Persons Exposed to Plutonium

For the direct epidemiology approach, the Russian workers exposed to plutonium provided the only risk estimates. These data are very well suited to estimating the risks from exposure to plutonium via inhalation because the exposure circumstances and exposure mode are virtually identical to those of interest in this report. The intrinsic merit of this approach is high and a score of 9 is assigned to it. (The score could perhaps be 10 but epidemiological methods, even if ideal, still have limitations compared with, say, physical measurements). The actual estimates that are derived from this approach are uncertain because the population was composed primarily of healthy adult male workers who are not representative of a U.S. population of both genders and all ages. Furthermore, the dose response did not include uncertainty in individual exposures or doses for which many details are lacking. Also individual smoking histories were not taken into account and smoking is a very serious confounder for studies of lung cancer. Because of these limitations this approach, although considered to have great intrinsic merit for estimating lung cancer risk, is comparatively uncertain.

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### **9.1.2 Intrinsic Merit of Epidemiologic Studies of Low-LET Radiation Combined with RBE factors**

The low-LET risk estimates that are derived from the Japanese atomic bomb survivors have the great advantage of being based on a very large population of all ages where follow-up has been virtually complete. However, that population received whole body exposure, more or less instantaneously, to a penetrating low-LET radiation. This approach inevitably relies heavily on the selection of appropriate values of RBE to account for the difference in biological effectiveness of alpha radiation as compared to gamma radiation. Fortunately, there is a very large pool of data upon which the RBE for alpha radiation can be based. Because the mode of exposure, exposure duration and radiation type differ fundamentally to the exposure circumstances for plutonium inhalation, the intrinsic merit of this indirect approach to risk estimation is not great. For this reason a score of 6 is given.

The differences in the quality of the Japanese atomic bomb survivor data and the RBE data for quantifying the risk for the four organs of interest for plutonium are reflected in the uncertainty estimates for this approach. The risk estimates for lung and bone marrow have smaller uncertainties than those for liver and especially bone.

### **9.1.3 Intrinsic Merit of Epidemiologic Studies of Populations Exposed to Other Alpha-Emitting Radionuclides**

The great advantage of the risk estimates derived from epidemiologic studies of humans exposed to alpha emitters other than plutonium is that individuals were exposed to the same radiation type. Thus consideration of the RBE of alpha radiation is not an issue. This approach is not scored as highly as the epidemiologic studies with plutonium but it is a relatively direct approach to risk estimation that has high intrinsic merit. A score of 8 is assigned to this approach.

The uncertainties in the risk estimates determined from this approach reflect a range of factors that vary in significance depending upon the organ of interest. These include differences in the physical and chemical characteristics of the alpha-emitting radionuclide as compared to plutonium, which lead to differences in the distribution of dose within the tissues and in exposure duration. They also include consideration of how representative the groups exposed to other alpha-emitters were of a U.S. population as a whole.

### **9.1.4 Intrinsic Merit of Controlled Studies of Animals Exposed to Plutonium and Other Alpha-Emitters and Extrapolation to Humans**

The positive features of the method of deriving risk estimates from animal studies are that the experiments were well controlled, exposures were mainly to plutonium supported by some other alpha-emitters, and smoking was not a confounder. However, the risk estimates are determined for species different from humans which significantly reduces the intrinsic merit of the approach. A score of 4 is assigned to the risk estimates from this approach.

**Table 9-2. Intrinsic Merit Scores ( $s_i$ )**

Risk estimation approach	Score ( $s_i$ )
Epidemiology with plutonium	9
Low-LET risk estimate with RBE factor	6
Human exposures to other alpha-emitters	8
Controlled studies of animals	4

### 9.1.5 Determination of Weighting Factors

The scores of intrinsic merit that are assigned to the different risk estimation approaches are summarized in [Table 9-2](#). These scores are used to calculate the factor by which each risk estimate is weighted before combining them to determine an overall risk estimate for a given cancer site. This weighting factor ( $w_i$ ) is determined according to the following equation,

$$w_i = \frac{s_i}{\sum_{i=1}^n s_i} \quad (9-1)$$

where

$s_i$  = score assigned to risk estimate  $i$

$n$  = number of independent risk estimates.

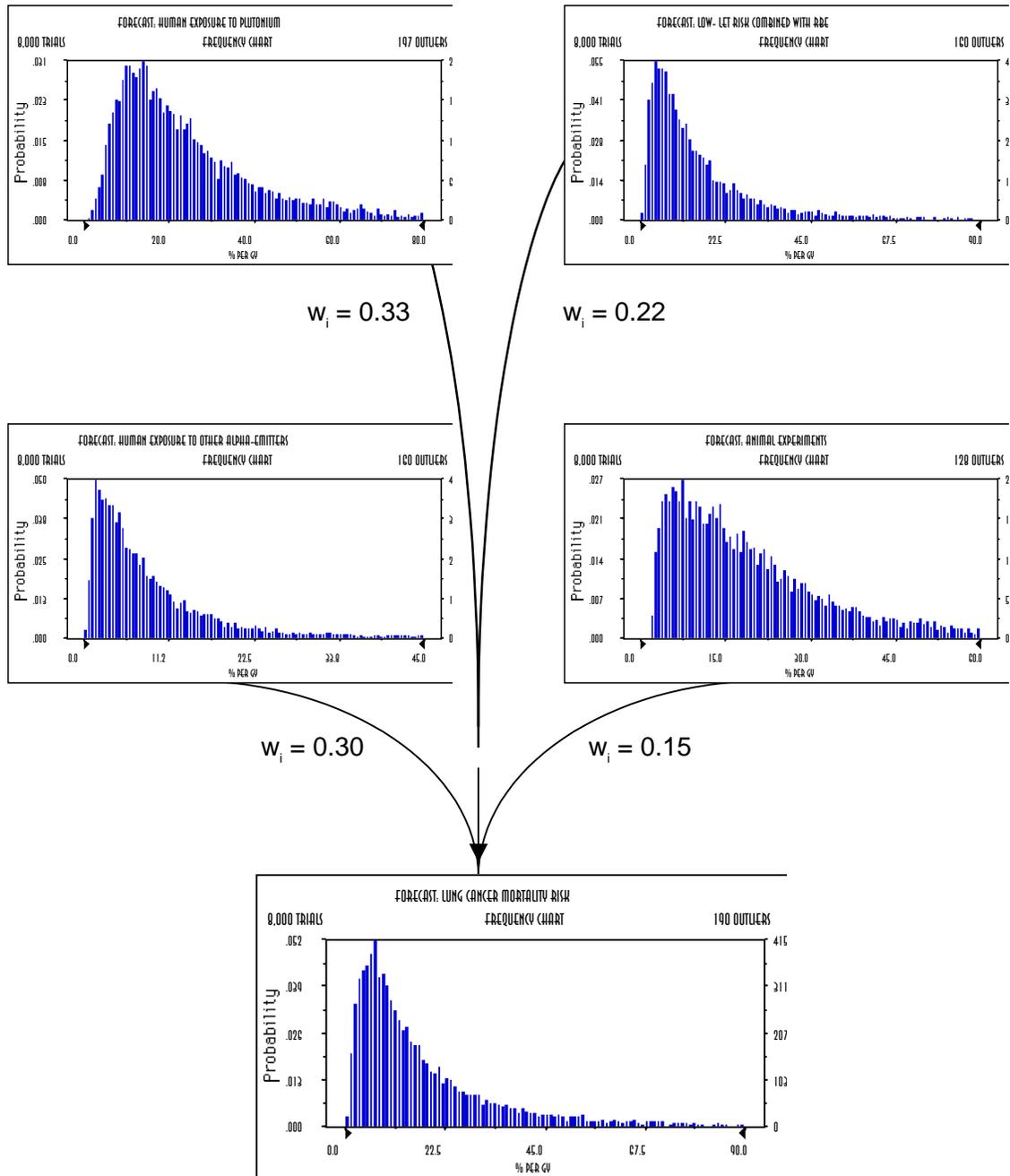
The weighting factors are summarized in [Table 9-3](#). The weight that is assigned to a given risk estimate approach depends on the number of approaches that provide a risk estimate. For example, there are four approaches that yield risk estimates for lung cancer whereas there are three risk approaches for bone cancer, liver cancer and leukemia (irradiation of bone marrow).

**Table 9-3. Risk Estimation Approach and Cancer Site Weighting Factors ( $w_i$ )**

Risk estimation approach	Cancer site	
	Lung	Liver, bone, bone marrow
Epidemiology with plutonium	0.33	–
Low-LET risk estimate with RBE factor	0.22	0.33
Human exposures to other alpha-emitters	0.30	0.45
Controlled studies of animals	0.15	0.22

## 9.2 Lifetime Cancer Mortality Risk Coefficients

The population-averaged lifetime risk of cancer mortality per unit dose from plutonium via inhalation for each cancer site is presented in [Table 9-4](#). These risk coefficients are calculated from the independent risk estimates summarized in [Table 9-1](#), weighted according to the values shown in [Table 9-3](#). [Figure 9-1](#) demonstrates the method used to combine the four distributions for the lung. In this case the distribution for approach 1 (workers exposed to plutonium) is sampled randomly 33% of the time; the distribution for approach 2 (low-LET risk estimate with RBE factor) is sampled randomly for 22% of the time; the distribution for approach 3 (other alpha-emitters) is sampled randomly for 30% of the time, and the distribution for approach 4



**Figure 9-1.** Schematic of methodology for calculation of the lifetime cancer mortality risk distribution from the risk estimate distributions for the four independent approaches weighted according to their intrinsic merit, taking lung cancer as an example.

(controlled animal experiments) is sampled randomly for the remaining 15% of the time. Overall, 8,000 iterations were made to generate the distribution of risk coefficients for each cancer site.

All the resulting distributions are positively skewed and suggest lognormal distributions in all cases except bone marrow, where the distribution is bimodal with both modes towards the lower end of the distribution. The largest mortality risk per unit dose is for lung cancer (Table 9-4). The median estimate is  $13 \times 10^{-2} \text{ Gy}^{-1}$  and there is about a factor of 40 difference between the 2.5 and 97.5 percentiles of the distribution. The mortality risk per unit dose for liver cancer is approximately one-half that for lung cancer. The median estimate is  $5.7 \times 10^{-2} \text{ Gy}^{-1}$  and there is about a factor of 70 difference between the 2.5 and 97.5 percentiles of the distribution. The median bone cancer mortality risk coefficient is  $0.13 \times 10^{-2} \text{ Gy}^{-1}$ , and the distribution is very large covering nearly three orders of magnitude. The median leukemia mortality risk coefficient is  $1.3 \times 10^{-2} \text{ Gy}^{-1}$ . This is an order of magnitude smaller than the median mortality risk coefficient for lung cancer and almost an order of magnitude larger than the median mortality risk coefficient for bone cancer. The uncertainty in the distribution is relatively large covering more than two orders of magnitude.

**Table 9-4. Distribution of U.S. Population Averaged Lifetime Cancer Mortality Risk Coefficients ( $10^{-2} \text{ Gy}^{-1}$ ) For Plutonium Exposure via Inhalation**

Cancer	Mortality risk coefficient distribution percentiles 50 (2.5–97.5) <sup>a</sup>
Lung	13 (1.5–67)
Liver	5.7 (0.84–60)
Bone <sup>b</sup>	0.13 (0.0029–4.2)
Bone marrow (leukemia)	1.3 (0.032–5.9)

<sup>a</sup> Values reported to 2 significant figures.  
<sup>b</sup> Based on dose to endosteal cells.

### 9.3 Comparison of Methods for Deriving Risk Coefficients

Assigning an intrinsic merit is subjective. We compared our methodology with three alternatives. First we asked the six experts who had critically reviewed the report to assign their scores for intrinsic merit ([Section 9.3.1](#)). Second we assigned an equal weight to the independent risk coefficients for each cancer site before combining them ([Section 9.3.2](#)). Finally, we estimated the risk coefficients that we might have calculated before this study using other available information from ICRP ([Section 9.3.3](#)). The conclusions that were drawn from these comparisons are presented in [Section 9.3.4](#).

#### 9.3.1 Solicitation of Scores of Intrinsic Merit From Six Expert Reviewers

As part of the scientific peer review process a draft version of this report was given to six experts with different backgrounds for critical review. After reviewing the report the experts were asked to provide their own best estimate of the scores of intrinsic merit. Regrettably, the experts saw the author's scores and weighting factors during their review, and this may have influenced their decisions. At that time, the definition of intrinsic merit was not as clearly defined and, as a consequence, scores were assigned for each cancer site for each approach. The

average weight that would be assigned based on the reviewers' scores is shown in [Table 9-5](#) and compared with the authors' weights (designated as Authors<sup>b</sup> in [Table 9-5](#)). In addition the range of weights that are determined from the experts' individual scores is shown in parentheses. Since that time intrinsic merit has been defined more precisely (see [Section 9.1](#)) which has resulted in the authors assigning a single score of intrinsic merit for each approach ([Table 9-2](#), see [Section 9.1](#)). The authors' final weights are given in [Table 9-5](#) for comparison (designated as Authors<sup>c</sup> in [Table 9-5](#)).

The experts' average weighting factors are very similar to those assigned by the authors especially for liver, bone and bone marrow ([Table 9-5](#)). The biggest difference occurs for the weight that is assigned to the second approach (the low-LET risk estimate combined with RBE factors) for the lung. We gave slightly less weight to this approach than the third approach which uses human exposures to other alpha-emitters. In contrast the experts assigned equal weight to both approaches or in two cases, a slightly higher weight to the second approach. Using the experts' average weighting factors yields essentially the same distribution of risk coefficients as those shown in [Table 9-4](#). The weighting factors from individual experts for a given approach vary by as much as a factor of 2 to 3 in some cases (see ranges in [Table 9-5](#)). This suggests the experts were not strongly influenced by the authors' initial estimates.

**Table 9-5. Comparison of Weighting Factors Assigned by Experts<sup>a</sup> and Authors**

Cancer	Epidemiology with plutonium	Low-LET risk estimate with RBE factor	Human exposures to other alpha-emitters	Controlled studies of animals
<b>Lung</b>				
Experts	0.31 (0.18–0.37)	0.29 (0.24–0.36)	0.25 (0.18–0.36)	0.15 (0.09–0.24)
Authors <sup>b</sup>	0.35	0.23	0.31	0.11
Authors <sup>c</sup>	0.33	0.22	0.30	0.15
<b>Liver</b>				
Experts	–	0.31 (0.23–0.47)	0.48 (0.37–0.62)	0.21 (0.15–0.33)
Authors <sup>b</sup>	–	0.31	0.50	0.19
Authors <sup>c</sup>	–	0.33	0.45	0.22
<b>Bone</b>				
Experts	–	0.30 (0.23–0.47)	0.49 (0.35–0.62)	0.21 (0.15–0.33)
Authors <sup>b</sup>	–	0.28	0.50	0.22
Authors <sup>c</sup>	–	0.33	0.45	0.22
<b>Bone marrow</b>				
Experts	–	0.41 (0.21–0.53)	0.43 (0.36–0.50)	0.16 (0.06–0.43)
Authors <sup>b</sup>	–	0.47	0.47	0.06
Authors <sup>c</sup>	–	0.33	0.45	0.22

<sup>a</sup> Average weight (range of weights).

<sup>b</sup> Weights assigned by authors at the time the experts reviewed the report.

<sup>c</sup> Weights subsequently assigned by authors.

### 9.3.2 Equal Weighting of Approaches

An alternative to assigning scores of intrinsic merit to each approach is to give each approach an equal weight. This removes any subjective bias in favor of or against any of the approaches that is introduced by assigning scores of intrinsic merit. The result of sampling each of the risk estimate distributions given in [Table 9-1](#) equally is shown in Table 9-6 and compared with the result of weighting the frequency of sampling from each approach according to the weights determined from the authors' scoring of intrinsic merit ([Table 9-3](#)).

**Table 9-6. Lifetime Mortality Risk Coefficients ( $10^{-2}$  Gy $^{-1}$ ) Obtained by Weighting the Independent Risk Coefficient Distributions Equally as Compared with Weighting According to the Scores of Intrinsic Merit<sup>a</sup>**

Cancer site	Equal weighting of risk estimate approaches	Weighting according to scores of intrinsic merit
Lung	13 (1.6–65)	13 (1.5–67)
Liver	8.2 (0.92–62)	5.7 (0.84–60)
Bone <sup>b</sup>	0.18 (0.0040–4.1)	0.13 (0.0029–4.2)
Bone marrow	0.91 (0.018–5.8)	1.3 (0.032–5.9)

<sup>a</sup> 50th percentile of distributions are shown with 2.5 and 97.5 percentiles in parentheses.  
<sup>b</sup> Based on dose to endosteal cells.

The distributions that are determined using the two different approaches are in fairly close agreement. For lung there is essentially no difference between the two distributions. This is not surprising because the four input distributions ([Table 9-1](#)) are quite similar. For liver, the median estimate for the approach that gives equal weight to the input distributions is about 40% larger than the median estimate for the approach that uses the scores of intrinsic merit. This difference arises because the intrinsic merit approach assigns more weight to the risk estimate distribution from human exposures to other alpha-emitters, and the median and 97.5 percentiles of this distribution are somewhat smaller than for the other two input distributions ([Table 9-1](#)). Despite the difference in the median estimates, the range of both distributions is almost the same. For bone, the situation is very similar to that for liver. The range of both distributions is almost the same, but the median estimate for the approach that gives equal weight to the three input distributions is about 40% larger than the median estimate for the approach that uses the scores of intrinsic merit. Again, this difference arises because the intrinsic merit approach assigns more weight to the risk estimate distribution from human exposures to other alpha-emitters, and the 97.5 percentile of this distribution is only equal to about the 50th percentile values of the other two input distributions ([Table 9-1](#)). For bone marrow, the situation is reversed compared to liver and bone. The median estimate for the approach that gives equal weight to the input distributions is about 30% smaller than the median estimate for the approach that uses the scores of intrinsic merit. Again this difference arises because the intrinsic merit approach assigns more weight to the risk estimate distribution from human exposures to other alpha-emitters, for which the 2.5 percentile value exceeds the 97.5 percentile value for the input distribution from controlled animal studies ([Table 9-1](#)). The input distribution from the low-LET risk estimate combined with RBE factors is very similar to the risk estimate distribution from human exposures to other alpha-

emitters. Consequently, the range of both distributions calculated using the two different approaches is similar. The conclusion from this comparison is that the results are quite robust and not highly dependent on the assignment of intrinsic merit scores.

### 9.3.3 Risk Estimates Calculated Using Other Available Information

ICRP provides point estimates of risk for use in radiation protection both for total cancer (for a whole population and for adult workers) and for a variety of organs and tissues, see Table 4, ICRP 60 (ICRP 1991). For lung and bone marrow these are obtained from the LSS of the atomic bomb survivors. The liver and bone risk estimates are obtained from alpha-emitter exposures. The ICRP risk estimates are for exposures to low LET radiations at low doses and dose rates and they relate to a population of equal numbers of both genders and a wide range of ages. The ICRP recommends a radiation weighting factor of 20 for alpha particles (ICRP 60, Table 1). The risk coefficients that would be derived from ICRP for plutonium exposure are shown in Table 9-7 where they are compared with the risk coefficient distributions determined in this study.

**Table 9-7. Comparison of Lifetime Cancer Mortality Risk Coefficients ( $10^{-2} \text{ Gy}^{-1}$ )**

Cancer site	This study (2.5–97.5 percentiles)	ICRP 60 (Low LET risk $\times$ RBE)
Lung	13 (1.5–67)	17 ( $0.85 \times 20$ )
Liver	5.7 (0.84–60)	3 ( $0.15 \times 20$ )
Bone <sup>a</sup>	0.13 (0.0029–4.2)	1 ( $0.05 \times 20$ )
Bone marrow	1.3 (0.032–5.9)	10 ( $0.50 \times 20$ )

<sup>a</sup> Based on dose to endosteal cells.

For the lung the comparison is very favorable. For the liver, the ICRP result is also favorable. The ICRP value is less than a factor of two smaller than the median estimate of the distribution determined in this study. However, the ICRP low LET risk estimate is known to be somewhat doubtful. A more recent estimate from the LSS (UNSCEAR 1994) gives a risk of  $60 \times 10^{-4} \text{ Gy}^{-1}$  for liver cancer which yields a risk estimate of  $12 \times 10^{-2} \text{ Gy}^{-1}$  assuming a RBE of 20 for exposure to plutonium. This value is about a factor of two larger than the median estimate of 5.8. Given the large uncertainty distribution for the liver risk estimate the agreement with ICRP and UNSCEAR is good. For bone the ICRP value of  $1 \times 10^{-2} \text{ Gy}^{-1}$  is approximately 7 times larger but well within the broad uncertainty bounds for our estimate.

For bone marrow the ICRP value is nearly an order of magnitude larger than the median estimate of the distribution determined in this study, and roughly a factor of 2 larger than the 97.5 percentile of the distribution, but only if the RBE is equal to 20. The plutonium risk estimate distribution determined in this study using the second approach (low-LET risk coefficient combined with RBE factor) was obtained using a distribution of lower RBE values. Using a median estimate of 3 for the leukemia RBE, as recommended in this study, results in a value of  $1.5 \times 10^{-2} \text{ Gy}^{-1}$  (i.e.  $0.5 \times 10^{-2} \text{ Gy}^{-1} \times 3$ ) that is in good agreement with our median value of  $1.3 \times 10^{-2} \text{ Gy}^{-1}$ .

### 9.3.4 Conclusions

Three comparisons were used to examine our methodology for combining the independent risk coefficient distributions: solicitation of scores of intrinsic merit from experts, assigning equal weight to the independent risk coefficient distributions, and comparing the risk coefficients with those expected from ICRP. The results are in surprisingly good agreement and well within the estimated uncertainty ranges. However, it should be noted that for bone marrow the risk estimates for leukemia are in good agreement only if an RBE of 3 (as we have recommended here) is used for this endpoint.

As a result of these comparisons, we conclude that our method of combining the independent risk distributions is valid. The risk coefficients presented in [Table 9-4](#) are considered best estimates of the distributions and are used in our analysis.

### 9.4 Lifetime Cancer Incidence Risk Coefficients

It is the risk of cancer incidence rather than the risk of cancer mortality associated with plutonium releases to the environment from the Rocky Flats Plant that is of interest in this study. The incidence risk for a given organ or tissue is obtained by dividing the mortality risk by the lethality fraction (unitless) given in Table 9-8. The survival data used in the analysis are for Colorado and are determined from cases diagnosed over the period 1974 through 1991, see also [Table 4-2](#) and [Figure 4-2](#).

$$\text{Lethality fraction} = [100 - \text{relative survival rate (\%)}] \div 100 \quad (9-2)$$

The relative survival rate is the observed survival rate adjusted for expected mortality from other causes. The relative survival rate represents the likelihood that a patient will not die from causes associated specifically with their cancer at some specified time after diagnosis. It is always larger than the observed survival rate for the same group of patients (NCI 1995). A complete time series of Colorado survival data are not available for liver and bone (see [Figure 4-2](#) presented earlier). Reliable survival data were available for up to 15 years after diagnosis for bone and for up to 5 years after diagnosis for liver. These data were fitted with power functions to obtain 20-year survival estimates.

**Table 9-8. Lethality Fractions Determined from Survival Rates for Colorado Based on Follow-up Data for 1974 through 1991 (Finch 1996).**

Cancer site	% Survival rate (% std error)	Lethality Fraction (-)
Lung	3.7 (0.2)	0.96
Liver	2.1 (0.6)	0.98
Bone <sup>a</sup>	50.0 (1.4)	0.50
Bone marrow (leukemia)	23.5 (0.6)	0.76

<sup>a</sup> Based on dose to endosteal cells.

The distribution of lifetime cancer incidence risk coefficients for each cancer site is calculated from the distribution of lifetime cancer mortality risk coefficients summarized in

[Table 9-4](#), divided by the lethality fraction in [Table 9-8](#). Uncertainty in the lethality fraction is included in the calculations and is propagated based on the uncertainty in the survival rates. The following coefficients of variation were determined for the Colorado survival data and used in the calculations: lung 15%, liver 25%, bone 20%, all leukemia except CLL 10%. The results of these calculations are summarized in [Table 9-9](#).

Both lung and liver cancer have high lethality fractions so the incidence risk ([Table 9-9](#)) is only a little greater than the mortality risk ([Table 9-4](#)). For leukemia, the survival rate for all leukemias except CLL was used because CLL is not believed to be induced by radiation ([Tomonaga et al.](#) 1991). The incidence risk of radiation induced leukemia is approximately 25% larger than the mortality risk. Of the cancer sites of interest for this study, bone cancer shows the largest difference between the mortality and incidence risk estimate, the bone cancer incidence risk is twice the mortality risk.

**Table 9-9. Population Averaged Organ-specific Lifetime Cancer Incidence Risks per Unit Dose ( $10^{-2}$  Gy $^{-1}$ ) for Plutonium Inhalation**

Cancer site	Distribution percentiles <sup>a</sup>
	50 (2.5–97.5)
Lung	14 (1.6–79)
Liver	6.1 (0.85–74)
Bone <sup>b</sup>	0.27 (0.0055–14)
Bone marrow (leukemia)	1.7 (0.042–8.2)

<sup>a</sup> Values reported to 2 significant figures.  
<sup>b</sup> Based on dose to endosteal cells.

The risk coefficients in [Table 9-9](#) are per unit dose to each organ. Because plutonium does not distribute uniformly among these organs, the risk per unit intake of activity better represents the inhalation exposure risk for each organ. The risk per unit intake is determined by combining the inhalation dose coefficients presented in [Chapter 3](#) and summarized in [Table 9-12](#) with the risk coefficients shown above in [Table 9-9](#). The results are discussed and presented at the end of [Section 9.6](#) in [Tables 9-13](#), [9-14](#) and [9-15](#).

### 9.5 Age and Gender Dependence of Risk Coefficients

Two factors that may influence the lifetime risk coefficients are age at exposure and gender. These two factors are discussed in detail in [Sections 4.7](#) and [4.8](#) of this report. From these discussions it is concluded that the data allow a distinction to be made between the risks and uncertainties to those under 20 years of age at exposure compared to those 20 and older for some of the cancer sites. A more detailed analysis is not considered warranted because of the lack of age-specific risk data for the cancer sites of concern. For some cancer sites the data also allow a difference in risk coefficients for males and females to be distinguished.

Where the difference in the median risk estimate between the two categories identified for age at exposure or for gender is judged to be less than a factor of 2, no adjustment is made to the population lifetime risk estimate distribution for that factor. This is the case for lung and leukemia (bone marrow) for both factors. However, the uncertainty in the population lifetime risk estimate due to each factor is still accounted for in the calculations. For lung the median

population lifetime risk estimate is considered uncertain by up to a factor of 2 in either direction with regard to age at exposure and gender. For leukemia the median population lifetime risk estimate is considered uncertain by up to a factor of 1.5 in either direction for both factors. A summary of the adjustment factors and uncertainties for age at exposure and gender is given in Table 9-10 where R represents the median population-average lifetime risk estimate. The values in parentheses indicate the 2.5 and 97.5 percentiles of the distribution for the parameter. All parameters are fit with a normal distribution except for the liver where a lognormal distribution is used. The fraction of the population under age 20 is based upon statistics for the current Colorado population where 30% of the population is under 20 years and 70% are 20 years or older. This is very similar to the U.S. population as a whole. The population consists of equal numbers of males and females.

**Table 9-10. Summary of Adjustments<sup>a</sup> for Age at Exposure and Gender Applied to the Population Lifetime Cancer Risk Estimate Distribution**

Cancer site	Age at exposure <sup>b</sup>		Gender <sup>c</sup>	
	Under 20	20 and over	Male	Female
Lung	R (0.59R–1.5R)	R (0.77R–1.2R)	R (0.67R–1.3R)	R (0.67R–1.3R)
Liver	1.5R (R–1.9R)	0.77R (0.63R–R)	1.3R (R–1.8R)	0.67R (0.22R–R)
Bone	1.5R (R–2.1R)	0.77R (0.53R–R)	1.3R (R–1.6R)	0.67R (0.4R–R)
Bone marrow	R (0.74R–1.3R)	R (0.87R–1.1R)	R (0.8R–1.2R)	R (0.8R–1.2R)

<sup>a</sup> R = median population lifetime risk estimate. Values in parentheses indicate 2.5 and 97.5 percentiles of distribution of adjustment uncertainties.

<sup>b</sup> Based on the Colorado population where 30% of the total population is under 20 and 70% is 20 and over.

<sup>c</sup> The population consists of equal numbers of males and females.

## 9.6 Final Risk Coefficients

The distributions of lifetime cancer incidence risk coefficients for each cancer site depending on age at exposure and gender ([Table 9-11](#)) are calculated from the distribution of lifetime cancer incidence risk coefficients summarized in [Table 9-9](#), multiplied by the gender and age at exposure adjustment factor distributions in [Table 9-10](#). For lung cancer and leukemia (bone marrow exposure), the risks to males and females are assumed to be equal. Also, the risks to people over 20 years of age at exposure are determined to be essentially the same as the risks to people under 20 years of age at exposure. For liver cancer and bone cancer the largest risk coefficients are calculated for males under 20 years of age at exposure. These risks are approximately twice those to males over 20 years of age at exposure or females under 20 years of

age at exposure. The lowest risk coefficients are estimated for females over 20 years of age at exposure. On average, this risk is roughly one quarter the risk to males under 20. However, the uncertainty distributions for all four risk coefficients overlap. The magnitude of the uncertainties is very similar to those seen in the mortality risk coefficients ([Table 9-4](#)). Although the population-averaged lifetime liver cancer incidence risk coefficients are roughly one-half the population-averaged lifetime lung cancer incidence risk coefficients, the liver cancer risk coefficients for males under 20 years of age at exposure are estimated to be very similar to the lung cancer incidence lifetime risk coefficients for any individual in the population.

**Table 9-11. Lifetime Cancer Incidence Risks per Unit Dose ( $10^{-2}$  Gy $^{-1}$ )**

Cancer site	Gender	Lifetime incidence risk distribution percentiles <sup>a</sup>	
		under 20	20 and over
Lung <sup>b</sup>	males/ females	13 (1.4–90)	13 (1.4–86)
Liver	males	12 (1.5–150)	6.3 (0.81–80)
	females	5.7 (0.60–80)	3.0 (0.32–41)
Bone	males	0.52 (0.011–29)	0.27 (0.0056–15)
	females	0.25 (0.0052–14)	0.13 (0.0026–7.4)
Bone marrow	males/females	1.7 (0.041–9.3)	1.7 (0.041–8.7)

<sup>a</sup> 50th percentile with 2.5 and 97.5 percentiles in parentheses, values reported to 2 significant figures.

<sup>b</sup> No account has been taken of the issue of smoking because of lack of information with which to do so.

An alternative way to present the lifetime cancer incidence risk estimates is per unit intake of activity rather than per unit dose to the organ or tissue. The risk per unit intake of activity is calculated by multiplying the dose per unit activity (or dose conversion factor) by the risk per unit dose (risk coefficient). For historical releases from the Rocky Flats site, inhalation of plutonium particles is identified as the primary exposure pathway for members of the public. As discussed in [Chapter 2](#) of this report, three different particle size distributions are used in the analyses to characterize the historical releases of plutonium from Rocky Flats. These have AMADs of 1  $\mu\text{m}$ , 5  $\mu\text{m}$  and 10  $\mu\text{m}$ . In all cases the inhaled plutonium is assumed to be in the oxide form. For releases from the 903 Area the range of plutonium-bearing dust particles to which a person may have been exposed is characterized by an AMAD of 5  $\mu\text{m}$  and a geometric standard deviation of 2.5. For routine vent and stack effluents including leakages, a plutonium aerosol with an AMAD of 1  $\mu\text{m}$  and a GSD of 2.5 is assumed. The size characteristics of plutonium particles released during the two fires is very uncertain, therefore a combination of all three particle size distributions is considered to cover the broad range of particle sizes in those discharges.

In [Chapter 3](#) the uncertainty in the dose conversion factors for the four organs of interest resulting from inhalation of a unit activity of plutonium aerosols with AMADs of 1  $\mu\text{m}$ , 5  $\mu\text{m}$  and 10  $\mu\text{m}$  (GSD = 2.5 in each case) is discussed in detail and is summarized here in [Table 9-12](#). The dose conversion factors are characterized by lognormal distributions with relatively large geometric standard deviations. The median absorbed dose received per unit activity of inhaled aerosol declines with increasing particle size ([Table 9-12](#)). The dose conversion factors for

inhalation of 1- $\mu\text{m}$  AMAD aerosols are roughly double those for inhalation of 5- $\mu\text{m}$  AMAD aerosols. Also, the uncertainties in the dose conversion factors increase with increasing particle size. The uncertainties in the dose conversion factors are smallest for the lung compared to the other organs.

**Table 9-12. Dose Conversion Factors for Plutonium Oxide Inhalation**

Cancer site	Dose conversion factor ( $\mu\text{Gy Bq}^{-1}$ ) for plutonium aerosols <sup>a</sup>		
	AMAD = 1 $\mu\text{m}$ <sup>b</sup>	AMAD = 5 $\mu\text{m}$ <sup>b</sup>	AMAD = 10 $\mu\text{m}$ <sup>b</sup>
Lung	4.4 (1.9)	2.6 (2.7)	1.2 (4.3)
Liver	2.0 (3.0)	0.95 (3.5)	0.42 (4.5)
Bone	9.0 (3.0)	4.6 (3.5)	2.1 (4.5)
Bone marrow	0.46 (3.0)	0.22 (3.5)	0.11 (4.5)

<sup>a</sup> Geometric mean is listed with geometric standard deviation in parentheses  
<sup>b</sup> Geometric standard deviation of each particle size distribution is 2.5

The distributions of lifetime cancer incidence risk per unit intake of activity that are calculated for the three particle size distributions are summarized in Tables [9-13](#), [9-14](#) and [9-15](#), respectively. The risk coefficients are presented per 100,000 persons per unit intake of activity in kilobecquerels (kBq). These numbers indicate the median number of cases of cancer (fatal and nonfatal) that would be expected to result from 100,000 people all inhaling one kilobecquerel of  $^{239}\text{Pu}$  particles with the defined particle size distribution. The 2.5 and 97.5 percentile values of the distributions are given in parentheses.

**Table 9-13. Lifetime Cancer Incidence Risk per 100,000 Persons per Kilobecquerel (kBq) of Inhaled  $^{239}\text{PuO}_2$ , AMAD = 1  $\mu\text{m}$ , GSD = 2.5**

Cancer site	Gender	Lifetime incidence risk <sup>a</sup> ( $10^{-5} \text{ kBq}^{-1}$ )	
		under 20	20 and over
Lung <sup>b</sup>	males/females	56 (4.1–590)	57 (4.5–570)
Liver	males	25 (1.2–740)	13 (0.62–380)
	females	12 (0.52–360)	6.3 (0.27–190)
Bone	males	4.4 (0.053–450)	2.3 (0.027–220)
	females	2.2 (0.023–230)	1.1 (0.013–120)
Bone marrow	males/females	0.65 (0.0099–15)	0.63 (0.0095–14)

<sup>a</sup> Median estimate (50th percentile) (2.5 and 97.5 percentiles of distribution), values reported to 2 significant figures.  
<sup>b</sup> No account has been taken of the issue of smoking.

The results for the inhalation of 1- $\mu\text{m}$  AMAD aerosols (Table 9-13) show that the highest lifetime cancer incidence risk per unit intake of activity is for lung. The median estimate is about  $57 \times 10^{-5} \text{ kBq}^{-1}$  with about an order of magnitude uncertainty in either direction. The large uncertainty results from the combination of the uncertainty in the dose conversion factor and the uncertainty in the risk coefficient. The second largest lifetime cancer incidence risk per unit intake of activity is for liver. The highest risk is to males under 20 years of age at exposure. The

median estimate is  $25 \times 10^{-5} \text{ kBq}^{-1}$  with more than a factor of 20 uncertainty in either direction. The differences in risks associated with age at exposure and gender mirror those seen for the risk per unit dose discussed in the previous section. The median estimates of lifetime cancer incidence risk per unit intake of activity for bone are about a factor of five smaller than for liver; however, the uncertainties are large and the upper 97.5 percentile values are about 60% of the 97.5 percentile values for liver. The increased significance of bone cancer incidence expressed as risk per unit intake of activity as compared to risk per unit dose reflects its large dose conversion factor relative to the other organs (Table 9-12). The bone dose conversion factor is twice that for lung. The smallest lifetime cancer incidence risk per unit intake of activity is for bone marrow (all leukemias except CLL). The median estimate is about  $0.65 \times 10^{-5} \text{ kBq}^{-1}$ . The distribution of uncertainties is positively skewed and is bimodal with both modes towards the lower end of the distribution. There is approximately three orders of magnitude difference between the 2.5 and 97.5 percentiles of the distribution.

The median lifetime cancer incidence risks from inhalation of 5- $\mu\text{m}$  and 10- $\mu\text{m}$  AMAD aerosols (Tables 9-14 and 9-15) follow the same trends as the 1- $\mu\text{m}$  AMAD aerosols, but are smaller in proportion to the smaller dose conversion factors (Table 9-12). The geometric standard deviation for the dose conversion factor increases significantly for the largest particle size distribution (10- $\mu\text{m}$  AMAD) leading to very large uncertainties in the risk estimates.

**Table 9-14. Lifetime Cancer Incidence Risk per 100,000 Persons per Kilobecquerel (kBq) of Inhaled  $^{239}\text{PuO}_2$ , AMAD = 5  $\mu\text{m}$ , GSD = 2.5**

Cancer site	Gender	Lifetime incidence risk <sup>a</sup> ( $10^{-5} \text{ kBq}^{-1}$ )	
		under 20	20 and over
Lung <sup>b</sup>	males/females	32 (1.5–500)	32 (1.6–490)
Liver	males	12 (0.44–450)	6.5 (0.23–230)
	females	5.8 (0.19–220)	3.1 (0.098–110)
Bone	males	2.3 (0.023–280)	1.2 (0.012–140)
	females	1.1 (0.011–130)	0.57 (0.0056–70)
Bone marrow	males/females	0.31 (0.0042–7.8)	0.31 (0.0042–7.7)

<sup>a</sup> Median estimate (50th percentile) (2.5 and 97.5 percentiles of distribution), values reported to 2 significant figures.

<sup>b</sup> No account has been taken of the issue of smoking.

**Table 9-15. Lifetime Cancer Incidence Risk per 100,000 Persons per Kilobecquerel (kBq) of Inhaled  $^{239}\text{PuO}_2$ , AMAD = 10  $\mu\text{m}$ , GSD = 2.5**

Cancer Site	Gender	Lifetime incidence risk <sup>a</sup> ( $10^{-5}$ kBq <sup>-1</sup> )	
		under 20	20 and over
Lung <sup>b</sup>	males/females	15 (0.43–500)	15 (0.46–490)
Liver	males	5.5 (0.15–260)	2.9 (0.077–130)
	females	2.6 (0.065–120)	1.4 (0.034–67)
Bone	males	1.1 (0.0082–150)	0.56 (0.0041–80)
	females	0.53 (0.0041–78)	0.27 (0.0021–41)
Bone marrow	males/females	0.15 (0.0016–5.9)	0.15 (0.0017–5.6)

<sup>a</sup> Median estimate (50th percentile) (2.5 and 97.5 percentiles of distribution), values reported to 2 significant figures.

<sup>b</sup> No account has been taken of the issue of smoking.

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