CHAPTER 6

DOSE AND RISK ESTIMATION

6.1 INTRODUCTION

Ionizing radiation emitted by the radioactive decay of nuclides released into the environment poses a risk of inducing excess cancers or heritable genetic effects in exposed humans. The curie (Ci) and becquerel (Bq) are units used to measure the activity of radioactive material, i.e., the rate atoms are giving off radiation or disintegrating. The curie is equal to 37 billion disintegrations per second, while the becquerel is equal to one disintegration per second. Exposure can occur through several "pathways," including inhalation, ingestion, or external irradiation by radionuclides in the air or deposited on the ground (see Chapter 8).

The risk of a health effect being induced in an exposed individual by a given exposure is calculated by first estimating the radiation dose to sensitive tissues in the individual, as a function of age. Depending on the radionuclide in question, its chemical form, and the exposure pathway, its distribution will vary within the body and with time, leading to a variation in radiation dose with organ and across time. The dose per unit exposure is referred to as a "dose conversion factor" (DCF). From the tissue-specific doses, the risks of a radiation-induced cancer, cancer death, or genetic effect are calculated using age- and organ-specific "risk factors." The dose conversion and risk factors are generally calculated from models, as outlined below. The number of excess cancers in a population is projected using a life-table calculation (BUN81, EPA94), which corrects for competing causes of death.

6.2 DOSE ESTIMATION

The risk of inducing a cancer in a specific tissue or organ increases with the absorbed dose, i.e., the amount of ionization and excitation energy per unit mass deposited in that tissue or organ. The risk of inducing a genetic effect increases with dose to the testes or ovaries. The absorbed dose, D, is expressed in gray (Gy) or rad, where 1 Gy = 100 rad. The risk also depends on the density of ionizations (the number of ionizations per unit path length) produced by the radiation. The density of ionizations is directly related to the "linear energy transfer" (LET), which is a measure of the amount of energy per unit path length deposited by a charged particle track in traversing a material. When the density of ionizations is high, the radiation is referred to as "high-LET"; conversely, "low-LET" radiation refers to that which is sparsely ionizing.

Accordingly, a derived quantity called the *effective dose* is introduced, which is expressed in units of sieverts (Sv) or rem. The effective dose in a tissue is given by Q×D, where Q is a quality factor (unitless) defined for a specific type of radiation.

Note that the absorbed dose is a physical quantity, but that the effective dose is a regulatory concept determined in part by the choice of Q. Values for Q are assigned based on radiobiological information on the relative biological effectiveness (RBE) of different types of radiation. Since the RBEs of different types of radiation are not known precisely, the assignment of Q rests heavily on the subjective judgments of experts on the ICRP. This document is concerned only with: (1) low-LET radiation from beta particles, gamma rays, or energetic X-rays, for which Q is taken to be unity and (2) high-LET alpha particles for which Q is taken to be 20 (ICR91, EPA94). In the case of low-LET radiation, 1 Sv = 1 Gy, and 1 rem = 1 rad. It follows that 1 Sv = 100 rem.

For regulatory purposes, it is useful to introduce certain other measures of "dose." First, there is the concept of the *effective dose equivalent* (EDE), which allows one to combine the dose equivalents to different organs into a single quantity. In this connection, each target organ, *i*, is assigned a weighting factor, w_i, which roughly represents the estimated proportion of the risk from a uniform, whole-body irradiation occurring in that particular organ. The effective dose equivalent is then the weighted sum of doses to the individual organs (ICR77):

$$EDE = \sum Q \times w_i \times D_i$$

Second, in dealing with internally deposited radionuclides that remain in the body and irradiate tissues for extended periods of time, the concept of "*committed dose*" is introduced (ICR77). For example, *the 50-yr committed effective dose equivalent* (CEDE) from a given intake is the calculated total EDE received over a 50-yr period following that intake. Finally, the *annual committed effective dose equivalent* (annual CEDE) refers to the CEDE resulting from one year's exposure or intake.

When the exposure is external, the dose calculation is a straightforward application of radiation physics. The radiation doses to target organs in an idealized "reference man" are calculated from the decay properties of the radionuclides and the well-understood interactions of radiation with matter (ICR79, EPA89).

For ingested or inhaled radionuclides, the dosimetry modeling is more complex. It is necessary to incorporate biokinetic information to describe the distribution and retention of the radionuclide (and any radioactive decay products) in the body as a function of time after intake. The irradiation of target tissues by internally deposited radionuclides is further complicated by the need to consider the cross irradiation of one tissue by radionuclides deposited in another tissue. Dosimetry models for internally deposited radionuclides have been developed by the International Commission on Radiological Protection (ICR79, ICR80, ICR81, ICR88). Dose conversion factors for internal and external radionuclide exposures are tabulated in EPA's Federal Guidance Reports Nos. 11 and 12, respectively (EPA88, EPA93). The individual protection standard of 25 mrem/yr that was developed under old dosimetry methods and used in the 40 CFR Part 191 standards promulgated in 1985 are essentially the same as the 15 mrem/yr (CEDE) standard for 40 CFR Part 197.

6.3 CANCER RISK ESTIMATION

EPA's current model for estimating radiogenic cancer risks incorporates age- and organ-specific risk coefficients for low-LET radiation based on data obtained from the Japanese atomic bomb survivors up through 1985, supplemented by organ-specific data from other sources (e.g., breast cancer induction in fluoroscopy patients). For most cancer sites, EPA's methodology involves an averaging of two sets of coefficients, reflecting two different ways of projecting risk from the atomic bomb survivors to the U.S. population, which have significantly different baseline rates of specific cancers (LAN91, EPA94, EPA99, EPA99a).

Aside from breast cancer, for which there is good epidemiological evidence that the dose response is approximately linear and independent of fractionation (NAS90), it was assumed that the risks at low doses and dose rates are reduced by a "dose, dose rate effectiveness factor" (DDREF) of 2 compared to the acute high dose exposures experienced by the bomb survivors. The value of 2 for the DDREF is consistent with ICRP recommendations (ICR91). For low dose (or dose rate) conditions, the calculated risk of a premature cancer death attributable to uniform, whole-body, low-LET irradiation is about 5.75×10^{-2}/Gy. Neglecting nonfatal skin cancers, which are usually not serious, the corresponding incidence risk estimate is 8.5×10^{-2}/Gy (EPA99a).

High-LET (alpha particle) risks are presumed to increase linearly with dose and to be independent of dose rate. Except for leukemia and breast cancer, a relative biological effectiveness (RBE) factor of 20 is adopted for estimating the risk of high-LET radiation relative

to that for low-LET radiation at low dose or dose rate conditions. Again the RBE value of 20 is consistent with the recommendations of the ICRP (ICR91). In view of epidemiological data on people ingesting or being injected with alpha-emitting radionuclides that deposit in bone, an effective RBE of 1 was adopted for leukemia; for breast cancer, the high-LET RBE of 10 is used to be consistent with the DDREF of 1 adopted for this site.

The lifetime excess risks of cancer incidence and mortality, for constant exposure rates to over 100 different radionuclides, are tabulated in the Final Version of EPA's Federal Guidance Report No.13 (EPA99). The dosimetry models employed in deriving these risk estimates reflect new ICRP recommendations and incorporate age-specific biological parameters (EPA99).

6.4 GENETIC EFFECTS

Genetic effects of radiation exposure are defined as stable, heritable changes induced in the germ cells (eggs or sperm) of exposed individuals, which are transmitted to and expressed only in their progeny across future generations.

The genetic risk of radiation exposure is more subtle than the somatic risk since it does not affect the persons exposed, but only their progeny. Somatic effects are expressed in the exposed individual over the person's remaining lifetime, while about 30 subsequent generations (nearly 1,000 years) are needed for near complete expression of genetic effects. Genetic risk is incurred by fertile people when radiation damages the DNA of the germ cells. The damage, in the form of a mutation or a chromosomal change, is transmitted to, and may be expressed in, a child conceived after the radiation exposure. However, the damage may also be expressed in some subsequent generation(s) or never.

Estimates of the genetic risk per generation are conventionally based on a 30-year reproductive generation. That is, the median parental age for conception of children is defined as age 30 (approximately one-half the children are produced by persons less than age 30, the other half by persons over age 30). Thus, the radiation dose accumulated from birth to age 30 is used to estimate the genetic risks. A basic assumption in assessing radiation genetic risk is that, at low doses and low dose-rates of low-LET radiation, there is a linear relationship between dose and the probability of occurrence of the genetic effect.

In the EPA Background Information Document for Radionuclides (EPA84), direct and indirect methods for obtaining genetic risk coefficients are described, and some recent estimates based on these methods are tabulated. Briefly, the direct method takes the frequency of mutation or occurrence of a heritable defect per unit dose observed in animal studies and extrapolates to what is expected for humans. These direct estimates are usually used for first generation effects estimates.

The EPA assessment of risks of genetic effects includes both first generation estimates and total genetic burden estimates. In developing risk coefficients for genetic effects, EPA has employed traditional definitions of genetic effects and dose-response relationships. Although the newly recognized mechanisms of genetic change listed above have future implications for genetic risk assessment, there are no data upon which to base radiation risk coefficients for these kinds of damage at this time.

In the NESHAPs Environmental Impact Statement (EPA89), the EPA estimated the low dose-rate, low-LET doubling dose for genetic effects to be 1.0 Gy (100 rad). That is, 1.0 Gy per reproductive generation (considered to be 30 years) would double the rate of occurrence of congenital defects (a defect existing at birth but not hereditary). However, at that time, the Agency indicated, based on limited human data, that the true doubling dose might be about three times greater. There is still no consensus on this point.

Neel and Lewis reviewed untoward pregnancy outcomes (UPOs) in the Japanese A-bomb survivors and compared them to mouse genetic effects data (NEE90a). The gametic doubling dose for low dose-rate, low-LET radiation in man, in this case, would be 400 rad (NEE90a). In a companion analysis of mouse genetic data, they estimated a gametic doubling dose in mice of 135 (16-400) rad. The gametic doubling dose for a study where only one sex was irradiated provides an analog of the “conjoint” parental gonadal dose for comparison purposes. However, for mice, they recommended a dose-rate factor of 3 for low dose-rate, low-LET radiation, so the doubling dose would also be 400 rad in mice (NEE90a).

UNSCEAR reviewed the recommendations listed above and concluded that the doubling dose in humans is most likely between 1.7 and 2.2 Sv (170 and 220 rad) for acute exposure to low-LET radiation, but 4.0 Sv (400 rad) for chronic exposure (UNS93). However, the UNSCEAR report also continued to estimate the hereditary effects of exposure to ionizing radiation using a doubling dose of 1.0 Sv (100 rad), just as in earlier UNSCEAR reports (UNS86, UNS88).

The EPA assumes a doubling dose of 100 rad (1 Sv) in this document, but again notes that some estimates of the doubling dose is about four times greater. The EPA estimate for equilibrium effects is about twice that of recent estimates by BEIR V and UNSCEAR because EPA included a value for equilibrium multifactorial effects where these others did not. The EPA estimates incorporate a dose-rate factor of 3 for low-LET radiation as reported in the 1977 UNSCEAR Report (UNS77).

The projected genetic effects attributable to a given population exposure depend on the population dynamics of future generations. However, if a stationary population is assumed, the number of effects can be derived from Table 6-1. The dose in the table is that received by parents in the first 30 years of life, the assumed generation period. Since the average lifetime of a person in the 1980 stationary population is about 75 years, 40 percent (30/75) of the population dose is considered to be genetically significant. Thus, to calculate genetic risk coefficients comparable to the cancer risk coefficients cited above, the values in Table 6-1 should be multiplied by 0.4. On this basis, eight serious heritable disorders are expected in the first generation following a 10^4 person-Gy population exposure of low dose (or dose rate), low-LET radiation, and 104 such effects would be expected over all generations. The number of serious genetic effects projected over all generations is then about 20 percent of the excess fatal cancers projected in the exposed population.

Table 6-1. Estimated Frequency of Genetic Disorders in a Birth Cohort Due to Exposure of Each of the Parents to 0.01 Gy (1 rad) per Reproductive Generation (30 yr)

Radiation	Serious Heritable Disorders (Cases per 10^6 Liveborn)	
	First Generation	All Generations
Low Dose Rate, Low-LET	20	260
High Dose Rate, Low-LET	60	780
High-LET	90	690

6.5 DEVELOPMENTAL EFFECTS

6.5.1 *In Utero* Carcinogenesis

Studies of the effects of *in utero* X-ray exposures in the U.K. in the 1960s showed increased childhood cancer as a sequela. The BEIR III Committee reviewed the data and estimated that there was a risk of 25×10^{-4} excess fatal leukemias per year per Gy exposure (25×10^{-6} per rad) and 28×10^{-4} excess fatal cancers of other types (28×10^{-6} per rad) (NAS80). The risk starts at birth and continues for 12 years for leukemias and 10 years for solid tumors (NAS80). Having reviewed additional data, the BEIR V Committee estimated that the risk was "... about 200 to 250 excess fatal cancer deaths $\times10^{-4}$ per Gy [200 to 250 $\times$ 10^{-6} per rad] in the first 10 years of life...." It also estimated one-half would be leukemias and one-quarter tumors of the nervous system (NAS90).

UNSCEAR estimated a risk of leukemia and solid tumors expressed during the first 10 years of life of 2×10^{-4} per rad (UNS86). The NRPB estimated a cancer risk of 2.5×10^{-4} cases of leukemia and 3.5×10^{-4} cases of solid tumors per rad of *in utero* exposure (STA88). The NRPB in 1993 retained the same cancer risk estimates but concluded about one-half the cases would be fatal and they would be expressed in the first 15 years of life (NRP93). However, the NRPB also estimated the lifetime risk would be four times greater than that of the first 15 years (NRP93).

6.5.2 Brain Teratology

The ICRP published an excellent review of the biology and the possible mechanisms of occurrence of radiation-induced brain damage *in utero* (ICR86). ICRP estimates: (1) for exposures from the 8th through the 15th week after conception, the risk of severe mental retardation is 4×10^{-1} per Gy (4×10^{-3} per rad), with a confidence interval of 2.5×10^{-1} to 5.5×10^{-1} per Gy (2.5×10^{-3} to 5.5×10^{-3} per rad) and (2) for exposures from the 16th through the 25th week after conception, the risk of severe mental retardation is 1×10^{-1} per Gy (1×10^{-3} per rad). However, a threshold below 50 rad could not be excluded (ICR86).

Effects other than mental retardation and microcephaly have been noted in the Japanese A-bomb survivors. Schull et al. (SCH88) reported that in individuals exposed prenatally between weeks 8 and 25 of gestation there is a progressive shift downward in IQ score with increasing exposure and that the most sensitive group is between 8 and 15 weeks gestational age at time of exposure. The BEIR V Committee estimated a 30 point loss in IQ per Gy exposure (0.3 points per rad)

consistent with a linear nonthreshold relationship (NAS90). However, even if the effect is linear-nonthreshold, the response would be too small to be detectable at environmental exposure levels.

Much the same pattern was reported for average school performance, especially in the earliest years of schooling (OTA88). Finally, a linear-nonthreshold relationship between exposure and incidence of unprovoked seizures in later life has been found to be consistent with the data for individuals exposed between 8 and 15 weeks gestational age (DUN88).

In 1986, the United Nations Scientific Committee on the Effects of Atomic Radiation also reviewed the question of mental retardation as a part of the overall review of the biological effects of prenatal radiation exposure (UNS86). UNSCEAR, like the ICRP, concluded there was a risk of severe mental retardation of 4×10^{-3} per rad over the period of 8 to 15 weeks after conception and of 1×10^{-3} per rad over the period 16 to 25 weeks after conception (UNS86).

The question of a threshold for central nervous system effects, particularly for the 8 to 15 week period of gestation, is unresolved. Apparent thresholds in the human data may merely reflect the statistical uncertainty due to the small number of cases. If, as has been suggested, the effects are due to improper synaptogenesis in the brain (temporal or spatial) (ICR86, OTA87), it should be noted that significant prolongation of cell cycle in matrix cells of the developing telencephalon in mice (exposed on day 13 of gestation) has been reported following exposures as low as 10 R (KAM78). Exposure of mice to 1 R on day 13 of gestation resulted in an increase in eye and brain abnormalities, but the increase was not statistically significant (MIC78).

6.5.3 Other Effects of Prenatal Irradiation

UNSCEAR estimated: (1) a pre-implantation loss of 1×10^{-2} per rad during the first two weeks after conception and (2) a malformation risk of 5×10^{-3} per rad during weeks 2 to 8 after conception (UNS86).

For many of the teratologic effects observed, no threshold has been demonstrated. If a teratogenic effect of radiation is due to cell-killing effects, then a threshold for that effect is probable. While early studies of radiation as a teratogen used high exposures and probably induced effects through cell killing, cell killing may not be required. Patrick cites Zwilling as follows: "... developmental anomalies appear to be caused by 'failure of proper tissue interaction to occur'" (PAT78, ZWI63). For example, a somatic mutation in a single cell, perhaps through

clonal expansion, could cause improper tissue interaction with no loss of cells; or, killing a single cell could cause release of a toxicant that causes an improper local interaction (RUS54, WEI54).

Jacobsen exposed pregnant mice to 0, 5R, 20R, or 100R on day 8 of gestation and scored skeletal abnormalities on day 19. He interpreted the dose-effect curve as linear or nearly so and saw no evidence of a threshold for the types of damage studied (JAC70). He stated: "The observations made, and in particular that concerning the apparent absence of a threshold dose, indicate that it is not justified to assume that irradiation with doses of 5 R and less is entirely without effect on the human embryo in early developmental stages" (JAC70). In another study, exposure of mice to 1 R on day 8 of gestation resulted in a significantly higher incidence of malformed and retarded fetuses compared to controls (MIC78). A 1981 review of data on the effects of ionizing radiation on the developing embryo/fetus reached essentially the same conclusions as Jacobsen (HHS81). Given the large number of experimental animals that would be required, direct evidence for a threshold below 5 rad will be difficult to provide.

6.5.4 Summary of Developmental Effects

EPA risk coefficients for estimating prenatal carcinogenic, teratologic, and nonstochastic effects in man (see Table 6-2) are, with one exception, the same as those published in the 1989 NESHAPs BID (EPA89). The first entry in the corresponding table in the NESHAPs BID lists "Fatal Cancer" as 6.0×10^{-4}. The entry should be for "Cancer Incidence." The fatal cancer risk is about half as great, 3×10^{-4}.

Table 6-2. Possible Effects of *In Utero* Radiation Exposure

Type of Risk to Conceptus	Risk per Rad
Cancer Incidence	$6x10^{-4}$
Mental Retardation[a] (exposure at 8-15 weeks)	$4x10^{-3}$
Mental Retardation[b] (exposure at 16-25 weeks)	$1x10^{-3}$
Malformation[b] (exposure at 2-8 weeks)	$5x10^{-3}$
Pre-implantation Loss (exposure at 0-2 weeks)	$1x10^{-2}$

[a] A threshold for mental retardation following exposure at 8-15 weeks of gestational age may depend on the mechanism of action.

[b] A threshold is expected for mental retardation following exposure during the 16-25 week period of gestation and for many types of malformations following exposures at early gestational age.

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