# 3. SUMMARY OF HEALTH EFFECTS OF IONIZING RADIATION

## 3.1 INTRODUCTION

Ionizing radiation is a form of radiation with sufficient energy to remove electrons from their atomic or molecular orbital shells in the tissues they penetrate (Borek 1993). These ionizations, received in sufficient quantities over a period of time, can result in tissue damage and disruption of cellular function at the molecular level. Of particular interest is their effect on deoxyribonucleic acids (DNA).

A special issue to consider when examining the health effects caused by ionizing radiation is the concept of dose and dose rate. The dose delivered to tissue from ionizing radiation can either be acute (the energy from the radiation is absorbed over a few hours or days) or chronic (the energy is absorbed over a longer period of months, years, or over a lifetime). The dose becomes particularly important when the individual is exposed is to radioactive materials inside the body. In distinguishing between acute and chronic exposure, both the intake rate and the physical, chemical, and biological aspects of the radionuclide kinetics must be considered. For radioactive materials with effective half-lives longer than a day, even if the intake is brief (minutes to a few days), the energy is deposited in tissue where it remains over a period longer than a few days, so that the exposure to the surrounding tissue is of a chronic duration. Depending on the size of the dose and the dose rate, the effects of ionizing radiation can either be acute (occurring within several hours to several months after exposure) or delayed (occurring several years after the exposure).

The principles of dose are important to the interpretation of Tables 8-1 through 8-4, found in Chapter 8 ("Levels of Significant Exposure to Radiation and Radioactive Material") in this profile. For example, Table 8-1 lists the observed health effects from radiation and radioactive material using inhalation as the route of exposure. Entry 109 shows a study in which Beagle dogs were exposed for 2 to 22 minutes to $^{90}SrCl_2$. Although these animals received the total amount of radionuclide within 2 to 22 minutes (an acute duration of exposure), the radionuclide was absorbed and redistributed to other tissues (in this case, bone), where it remained for a protracted period of time (chronic exposure). Delayed effects of osteosarcoma and other tumors were found in almost half of these animals (Gillett et al. 1987b). Without a clear understanding of both the dose and the toxicokinetics of the radionuclide, one might conclude from this table that a 2- to 22-minute dose of radiation from $^{90}SrCl_2$ will cause bone cancer in dogs. The more appropriate conclusion to draw from this study is that after a 2- to 22-minute intake, $^{90}SrCl_2$

appeared to have redistributed from the lungs to the bones and, given its long physical half-time ($t_{1/2}$) of 28.6 years, would have irradiated the surrounding tissues for a lengthy period of time to produce a cancerous end point.

Sources of ionizing radiation can be found at many waste sites in the United States and other countries. Exposure to these sources may have potential adverse health effects, depending on the isotope, the absorbed dose, and the dose rate. The predominant radionuclides found currently or in the past at Department of Energy (DOE) National Priorities List (NPL) waste sites are listed in Table 3-1.

**Table 3-1. ATSDR Priority Listing of Radionuclides Present at Department of Energy NPL Sites**

| Ranking # | Isotope | Primary emission | Physical half-life | Target tissue(s) for soluble forms |
|---|---|---|---|---|
| 1 | Thorium-232 | α | $1.4 \times 10^{10}$ years | |
| 2 | Uranium-235 | α | $7.04 \times 10^{8}$ years | Renal (proximal tubules)[a] |
| 3 | Radium-228 | β | 5.76 years | Skeleton |
| 4 | Uranium-238 | α | $4.46 \times 10^{9}$ years | Renal (proximal tubules) |
| 5 | Radium-226 | α | 1600 years | Skeleton |
| 6 | Cobalt-60 | β, γ | 5.271 years | Whole body |
| 7 | Krypton-85 | β | 10.72 years | |
| 8 | Americium-241 | α | 432.2 years | Lung |
| 9 | Uranium-234 | α | $2.45 \times 10^{5}$ years | Renal (proximal tubules) |
| 10 | Potassium-40 | β | $1.26 \times 10^{9}$ years | Skeleton |
| 11 | Europium-152 | β | 13.5 years | |
| 12 | Neptunium-237 | α | $2.14 \times 10^{6}$ years | |
| 13 | Cesium-137 | β,γ | 30 years | Whole body |
| 14 | Protactinium-231 | α | $3.25 \times 10^{4}$ years | |
| 15 | Strontium-90 | β | 28.6 years | Skeleton |
| 16 | Krypton-88 | β | 2.84 hours | |
| 17 | Thallium-208 | β | 3.053 minutes | |
| 18 | Thorium-228 | α | 1.913 years | |
| 19 | Protactinium-234 | β | 6.69 hours | |
| 20 | Argon-41 | β | 1.82 hours | |
| 21 | Plutonium-239 | α | 24,131 years | Bone surface |
| 22 | Krypton-87 | β/γ | 76.3 minutes | Whole body |
| 23 | Thorium-230 | α | 77,000 years | Bone surface |
| 24 | Uranium-236 | α | $2.3415 \times 10^{7}$ years | Bone surface |
| 25 | Plutonium-238 | α | 87.75 years | Bone surface |

[a]Renal toxicity is more likely due its heavy metal properties rather than its radioactive properties.
Source: Lide 1996; Schleien 1992

The scientific literature is filled with in-depth discussions and reviews on the effects of ionizing radiation in humans and animals, and it would be difficult, if not impractical, to summarize all of the known information about the effects of each radionuclide in every animal. Although the database of biological, radiological, toxicological, and toxicokinetic information is substantial and much is known, much remains to be learned about the specific mechanisms by which ionizing radiation produces its effects, how these effects can be minimized in living tissues, and what the long-term effects of very low doses of ionizing radiation are over the normal human lifespan. In this profile, some of the information about the effects of ionizing radiation has been obtained from human epidemiological and medical studies, but a sizable portion has come from studies conducted in laboratory animals and then extrapolated to humans. In addition to data from epidemiological studies, there is a substantial human database derived from therapeutic applications of radiation. Because of this large database of information, and in an effort to provide a useable overview of the health effects caused by exposure to radionuclides, this toxicological profile will summarize the adverse effects of ionizing radiation from alpha (α), beta (β), and gamma (γ) radiation, using representative radionuclides to illustrate the effects on specific organs and tissues. Other radionuclides with similar emissions and kinetics may produce similar end points. This profile will not provide an in-depth discussion of the more subtle points of radiation biology and toxicology. It will, however, provide the reader with a comprehensive and informative overview of a cross-section of the scientific literature that pertains to the potential adverse carcinogenic and non-carcinogenic effects of α, β, and γ radiation, focusing on key human and animal studies and using representative radionuclides for illustration purposes. Readers are encouraged to consult both the glossary and Chapter 2 of this profile to become familiar with the terminology used in discussing exposure to ionizing radiation and the characteristics of these three radiations. Several excellent texts and review papers are also available in the open literature that provide the salient background material for many of the sections of this profile (BEIR IV 1988; BEIR V 1990; Faw and Shultis 1993; Harley 1991; Roesch 1987; UNSCEAR 1993; Raabe 1994).

## 3.2 HEALTH EFFECTS FROM EXPOSURE TO IONIZING RADIATION

High doses of ionizing radiation can lead to various effects, such as skin burns, hair loss, birth defects, illness, cancer, and death. The basic principle of toxicology, “the dose determines poison,” applies to the toxicology of ionizing radiation as well as to all other branches of toxicology. In the case of threshold effects (“deterministic effects” in the language of radiation toxicology), such as skin burns, hair loss, sterility, nausea, and cataracts, a certain minimum dose (the threshold dose), usually on the order of hundreds or thousands of rad, must be exceeded in order for the effect to be expressed. An increase in the size of the dose above the threshold dose will increase the severity of the effect.

For cancer induction, increasing the radiation dose does not increase the severity of the cancer; instead it increases the chance of cancer induction. In the case of carcinogens generally, whether chemical or radiological, safety standards are based on a postulated zero threshold (i.e., any increment of carcinogen, no matter how small, is assumed to carry with it a corresponding increase in the chance of causing cancer). Increasing the size of the dose increases the probability of inducing a cancer with that carcinogen. Cancers that are, in fact, caused by radiation are completely indistinguishable from those that seem to occur spontaneously or are caused by other known or suspected carcinogens. In a given population, such as the Japanese survivors of the atomic bombings of 1945, investigators identified the carcinogenicity of ionizing radiation only by measuring the frequency of occurrence of cancer. In the case of the survivors of the atomic bombings in Japan, there was no observed statistically significant increase in cancer frequency among people whose radiation dose did not exceed 0.4 Gy (40 rad) and no increase in leukemia among those whose radiation dose did not exceed 0.1 Gy (10 rad). Because investigators could not uniquely identify any cancer as having been caused by the radiation, and because there was no observed increase in cancer frequency following low-level irradiation, the calculated cancer risk coefficient (i.e., the probability of getting cancer per unit of radiation dose) is usually estimated by extrapolation of data from observations on populations that received high doses of radiation.

For the purposes of this profile, we have divided the end points produced by ionizing radiation into effects that were (at least initially) non-carcinogenic and carcinogenic effects. The non-carcinogenic effects were further subdivided by major organ systems affected plus teratogenic effects. This was done primarily to help the reader understand the broad scope of adverse health effects that can be produced by ionizing radiation. This approach was also necessary to facilitate evaluating study designs found in the literature. Some studies exposed laboratory animals to radiation, determined the non-cancerous end points, and then sacrificed the animals to complete the study objectives. These studies imply that cancer did not or would not develop after exposure to this radiation, which certainly may not be the case. Other studies exposed animals to radiation, observed the non-carcinogenic end points (if any), and then allowed the animals to live out their normal lifespans to determine if cancer would develop. These latter studies provided more complete information on the overall effects of exposure to ionizing radiation.

No acute-, intermediate-, or chronic-duration inhalation, oral, or dermal Minimal Risk Levels (MRLs) were developed for internal exposure to alpha, beta, or gamma radiation. Radiation effect(s) on a biological system during an acute, intermediate, or chronic duration of exposure depend on the radiation dose; the dose, in turn, depends on several variables. For airborne radioactivity, these include physical form (gas versus particle), particle solubility, particle size, type of radiation (alpha, beta, gamma, or combinations), and energy of the radiation. For oral and dermal exposure, toxicity is influenced by

solubility, metabolism within the body, and the type and energies of the radiation. Since there is a biological equivalence of internal and external dose equivalent in units of sievert and rem, an MRL for external radiation should be appropriate for internal radiation.

Two MRLs have been derived for exposures to ionizing radiation:

- An MRL of 0.004 Sv (0.4 rem) has been derived for acute-duration external ionizing radiation exposure (14 days or less).

The acute MRL is based on results from two studies, one by Schull et al. (1988) and one by Burt (1966). Schull et al. (1988) evaluated the quantitative effect of exposure to radiation on the developing fetal and embryonic human brain. The end point measured was change in intelligence test scores. Broadly speaking, a large body of literature shows the effects of radiation on the embryonic and fetal brain. ATSDR recognizes that there is considerable public interest in and debate about the interpretation of intelligence scores and that government agencies have been very careful in setting health benchmarks for chemicals whose effects are measured by intelligence testing. ATSDR is basing the MRL on the published results from relevant IQ studies and applies a conservative factor to account for uncertainties. Underlying assumptions in the MRL development are stated as clearly as possible.

Schull et al. (1988) evaluated effects on individuals exposed *in utero* during the atomic bombing of Hiroshima and Nagasaki, based on the original PE86 samples (n=1,759; data on available intelligence testing) and the clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more, and many more individuals in the dose range 0–0.49 Gy than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 meters in Hiroshima and Nagasaki. Children prenatally exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki; the Koga test was conducted in Hiroshima. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or after the 25$^{th}$ week. The highest risk of radiation damage to the embryonic and fetal brain occurred 8 to 15 weeks after fertilization under both T65DR and DS86 dosimetric systems (Otake and Schull 1984). The regression of intelligence score on estimated DS86 uterine absorbed dose is more linear than with T65DR fetal dose, and the diminution in intelligence score under the linear model is 21–29 points at 1

Gy. The regression of intelligence score on estimated fetal absorbed dose was linear for the exposed 8–15 weeks after fertilization and possibly linear for the 16–25-week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure in the 8–25-week exposure group. The mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the groups exposed at 8–15 and 16–25 weeks.

The linearity of the response over the exposure ranges does not mean that there is no threshold for ionizing radiation's neurological effects. A threshold response (i.e., deterministic response) in the case of ionizing radiation involves damage to brain stem cells or to cells that differentiate into brain cells. This threshold, however, is indeterminate and therefore, there is no readily available lowest-observed-adverse-effect level (LOAEL). However, a no-observed-adverse-effect level (NOAEL) is taken from a study by Burt (1996). Results from the Schull et al. (1998) study are used in conjunction with the Burt (1966) study described below. The Burt study (1996) is the basis of a population IQ differential used to establish a NOAEL dose from the Schull et al. (1998) study.

The study by Burt (1966) determined differences in intelligence in monozygotic twins reared together (n=95) and apart (n=53). All tests were conducted in school and consisted of (1) a group test of intelligence containing both non-verbal and verbal items, (2) an individual test (the London Revision of the Terman-Binet Scale) used primarily for standardization and for doubtful cases, and (3) a set of performance tests based on the Pitner-Paterson tests and standardization. The methods and standard remained much the same throughout the study. The children were brought up by parents or foster parents (occupation ranged from unskilled to professional). The standard deviation of the group of separated monozygotic twins was reported at 15.3 as compared to 15.0 of ordinary siblings. Twins brought up in different environments were compared with those brought up in similar circumstances. The average IQ scores of the twins measured on a conventional IQ scale (SD=15) was 97.8 for the separated monozygotes, 98.1 for monozygotes brought up together. The difference of 0.3 IQ point between the separated and unseparated identical twins (97.8–98.1) is considered a NOAEL for this study.

Husen (1959) reported a study involving 269 pairs of Swedish monozygotic (identical) twins where the intrapair IQ difference was 4 IQ points for a combination of twins raised together and apart. This is somewhat lower than the value of 7 IQ points for identical twins raised apart, and just larger than the range of IQ scores for Washington DC children repetitively tested (Jacobi and Glauberman 1995).

Supporting evidence for the acute MRL is provided by Jacobi and Glauberman (1995). Children in the 1$^{st}$, 3$^{rd}$, and 5$^{th}$ grades born in Washington DC were tested, and average IQ levels of 94.2, 97.6, and 94.6

were reported. The differences of up to 3.4 IQ points between the grades and over time were considered to be small and could not be tied to environmental deficiencies. This difference is a potential LOAEL for acute doses of ionizing radiation and would yield an MRL of 0.004 Sv (3.4 IQ points x 1 Sv/25 IQ points ÷ 30 [10 for use of a LOAEL and 3 for a sensitive human population]).

Additional supporting evidence for the acute MRL is provided by Berger et al. 1997, in a case study of accidental radiation injury to the hand. A Mexican engineer suffered an accidental injury to the hand while repairing an x ray spectrometer. The day after the accident, his symptoms included a tingling sensation and itching in the index and middle fingers. On days 4 and 7, a "pinching" sensation, swelling, and slight erythema were observed. By day 7, the tip of his index fingers was erythematous and a large blister developed with swelling on other fingers. On day 10, examination by a physician showed that the lesions had worsened and the fingers and palms were discolored. On day 10, he was admitted to the hospital where hyperbaric oxygen therapy was administered without success. One month after the accident, the patient entered the hospital again with pain, discoloration, and desquamation of his hand. Clinical examination showed decreased circulation in the entire hand, most notably in the index and middle finger. Total white blood count decreased to 3,000/µL (normal range 4,300–10,800/µL). Cytogenic studies of peripheral blood lymphocytes revealed four dicentrics, two rings, and eight chromosomal fragments in the 300 metaphases studied. The estimated whole body dose was reported to be 0.382 Gy (38.2 rad). This dose is a potential LOAEL for acute ionizing radiation and would yield an MRL of 0.004 Sv (0.38 Sv ÷100 [10 for use of LOAEL and 10 for human variability]).

The Nuclear Regulatory Commission set a radiation exposure limit of 5 mSv (500 mrem) for pregnant working women over the full gestational period (USNRC 1991). For the critical gestational period of 8 to 15 weeks ATSDR believes that the acute MRL of 4 mSv is consistent with the NRC limit and could be applied to either acute (0–14 day) or intermediate (15–365 day) exposure periods.

The acute MRL is based on the finding that a 1 Gy dose (1 Sv dose equivalent) results in a 25 IQ point reduction (range = 21–29 points; mean = 25) (Schull et al. 1988). This assumes that the relationship between radiation dose and IQ point reduction is linear (Schull et al 1988). After applying an uncertainty factor of 3 (human variability/sensitive population), this results in an MRL of 0.004 Sv (0.4 rem).

There are recognized uncertainties in the results from both the Schull et al. (1998) and the Burt (1966) studies. Although the linear relationship developed for data from the Japanese fetal-exposed population is strong, it has not been established that the linear relationship holds all the way to the lowest potential exposure levels. Another important uncertainty is the selection of an appropriate population IQ shift that

could be accepted as a non-adverse effect. A change in median population IQ test results is far different from natural fluctuations in individual test results or from the natural variation in a population (e.g., standard deviation in population IQ of 15 points). Selection of a population shift of 0.3 IQ points is an understandably conservative, yet appropriate, approach in setting a health guideline for acute exposures to ionizing radiation. Though the IQ reduction end point is based on a sensitive population (8–25 week-old fetuses), ATSDR has applied an additional uncertainty factor of 3 for human sensitivity.

Our understanding of the health hazard posed by ionizing radiation will continue to expand and, therefore, be subject to change. As additional new information concerning the potential public health impact of ionizing radiation becomes available, ATSDR will evaluate that information. ATSDR will continue to work with our Federal partners to ensure an up-to-date assessment of all relevant biomedical data to protect the public from exposure to harmful levels of ionizing radiation. The acute MRL value is supportive of the Nuclear Regulatory Commission fetal protection dose equivalent of 5 mSv (500 mrem) during the gestation period. EPA has derived neither an RfD nor an RfC for ionizing radiation (IRIS 1999).

- An MRL of 1.0 mSv/yr (100 mrem/yr) above background has been derived for chronic-duration external ionizing radiation exposure (365 days or more).

No individual studies were identified that could be used to base a chronic-duration external exposure MRL that did not result in a cancer-producing end point. However, BEIR V (1990) reports that the average annual effective dose to the U.S. population is 3.6 mSv/yr. A total annual effective dose equivalent of 3.6 mSv (360 mrem)/year to members of the U.S. population is obtained mainly by naturally occurring radiation from external sources, medical uses of radiation, and radiation from consumer products. Since this annual dose of 3.6 mSv/yr has not been associated with adverse health effects or increases in the incidences of any type of cancers in humans or other animals, the 3.6 mSv/yr is considered a NOAEL for purposes of MRL derivation. An uncertainty factor of 3 (for human variability) was applied to the NOAEL of 3.6 mSv/yr to derive the MRL of 1.0 mSv/yr.

The chronic MRL value is supportive of the 1 mSv/yr (100 mrem/yr) dose equivalent limit to the public that is recommended by the International Commission on Radiological Protection and required by the Nuclear Regulatory Commission. The EPA has derived neither an oral RfD nor an inhalation RfC for ionizing radiation (IRIS 1999). EPA has derived limits for concentrations of selected radioactive materials in drinking water under the Safe Drinking Water Act. The population is simultaneously

exposed to radiation through oral, inhalation, and external routes of exposure, and the chronic MRL is applicable to the cumulative exposure by all routes.

### 3.2.1 Acute (Immediate and Non-Carcinogenic) Effects from Ionizing Radiation Exposure

A considerable body of information is available in the literature on the acute exposure, high-dose health effects of ionizing radiation. Such health effects would not be possible from levels of residual radioactive material at NPL sites. There are three circumstances in which a person may conceivably be exposed to acute high-level doses of ionizing radiation that would initially result in one or many immediate non-carcinogenic effects. One instance would involve being in the immediate proximity of an atomic blast, as were the Japanese populations of Hiroshima and Nagasaki in August 1945 or the Marshall Islands fallout victims injured from fallout from an atomic weapons blast on Bikini Atoll in March 1954. The second instance would be a laboratory or industrial accident, where only those onsite and involved with high intensity radioactive sources or radiation generating equipment would be affected. The third and most likely opportunity for exposure to high levels (or repeated doses) of ionizing radiation would involve medical sources in the treatment of disease (protracted exposures to x rays, fluoroscopy, radioiodine therapy, etc.) or exposure to displaced medical or industrial radiography sources. People who volunteer to be exposed to ionizing radiation for the purpose of medical research also fall into the third category (see Table 3-2). People who have a large enough area of their body exposed to high doses ($\geq$100 rad) of radiation in any of these situations may exhibit immediate signs known as acute radiation syndrome. In addition to radiation sickness, overexposure to ionizing radiation can result in lens opacities (~0.2 Gy threshold and protracted exposure), and fetal and developmental anomalies.

The acute and delayed effects of exposure to ionizing radiation in humans and laboratory animals have been studied quite extensively. Laboratory animal data have provided a large volume of information related to the health effects of radiation; however, the most useful information related to human health effects comes from human exposure data. The data collected from the larger exposed populations, such as those from Hiroshima and Nagasaki, some medically-exposed populations, or the radium dial painters, have provided valuable information on both the acute and the delayed (long-term) health effects in humans exposed to radiation from certain radionuclides. A number of studies performed on smaller groups of people as early as the 1930s have been recently identified and made public (DOE 1995). These experiments will not be discussed in depth in this toxicological profile (for reasons listed below), but will be briefly summarized. Most of these exposures to sources of ionizing radiation were performed in small

groups of human volunteers at a few institutions sponsored or supported by the Department of Energy (DOE), U.S. Energy Research and Development Administration (ERDA), the U.S. Atomic Energy Commission (AEC), the Manhattan Engineer District (MED), and the Office of Scientific Research and Development (OSRD). Other studies took place at universities, private hospitals, and other institutions. The bulk of these human studies may be categorized as either tracer studies, metabolism studies, dose-response studies, or as experimental treatments for disease. Many of the studies listed in the DOE report were done before the 1970s, so the 1995 report represents the culmination of significant efforts to assemble the appropriate documentation to reconstruct and describe the purpose of each experiment, the experimental designs, the dates and locations of the exposures, the doses and routes of administration, the population size and how the populations were chosen, the use of informed consent among these individuals, and whether any of these individuals were followed through the remainder of their life in order to determine possible delayed effects from exposures to these radionuclides. In spite of the problems associated with interpreting these experiments, they yielded a useful database of information that describes the health effects of radiation exposure in humans. Some of these studies are summarized in Table 3-2.

All cells that comprise the body's tissues and organ systems are not equally sensitive to the biological effects of ionizing radiation; the sensitivity of cells is affected by age at the time of exposure, sex, health status, and other factors. Cells that are rapidly growing and dividing (such as those found in the gastrointestinal tract, bone marrow, reproductive and lymphoid tissues, and fetal nerve cells) are more sensitive to the cytotoxic effects of ionizing radiation. Higher doses showed more effects in the gastrointestinal tract than in the bone marrow. Tissues that undergo little cell growth and mitosis under normal conditions (such as those found in the central nervous system, the adrenal, adipose, and connective tissues, and the kidney) are more resistant to these effects, requiring a much larger acute absorbed dose before outward toxicological effects may be observed. Why are these growing and dividing cells the most sensitive to the effects of ionizing radiation? The answer relates to the effect on the genome of the cell. Ionizing radiation may damage the cell's DNA (which the cell relies on to manufacture proteins and enzymes, perform routine cell functions, and maintain cell integrity and homeostasis) to the point that normal cell functions are markedly decreased or stopped, resulting in cell damage and death. Once damaged, the cell can either repair the damage or die. Repair or misrepair may or may not result in cell lethality. When precursor cells in the hematopoietic system (which multiply quite frequently to replenish aging leukocytes) are damaged or die, leukopenia may occur in the peripheral blood, leaving the body susceptible to infections and disease. At ~0.5 Gy (50 rad), there may be transient changes in formed elements of the blood in some individuals. At 1 Gy (100 rad), most individuals express transient

**Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides**

| Location | Year(s) | Radionuclide | Purpose of experiment | Number of people dosed | Dose and route of exposure | Result |
|---|---|---|---|---|---|---|
| ANL | 1931-1933 | $^{226}$Ra | Determine the retention time of $^{226}$Ra in humans | NA | 70–50 µg; injected | Incomplete |
| ANL | 1943-1946 | x rays; $^{32}$P | Determine effects of radiation, process chemicals and toxic metals in humans | 4 | x rays: 30 R $^{32}$P: route not specified | White blood cell chemistry was important in assessing the radiation sensitivity of workers exposed to radiation |
| ANL | 1944-1945 | $^{32}$P | Study the metabolism of hemoglobin in cases of polycythemia rubra vera | 7 | 15–40 µCi; route not specified | NA |
| ANL | 1962 | $^{3}$H | Study the uptake of $^{3}$H thymidine in tumors and the effects of $^{3}$H on tumors | 4 | 10 µCi; injected | Similar growth was noted in both cancerous and non-cancerous cells treated with $^{3}$H |
| ANL | 1943-1944 | x ray | Study hematological changes at varying doses of radiation in cancer therapy | 14 | 27–500 R; external exposure | Reduction of white blood cells formed in lymphoid tissue; routine monitoring of blood components not a practical way of assessing the usual occupational radiation exposures |
| ANL | 1948-1953 | $^{76}$As | Determine effects of $^{76}$As on hemato-poietic tissues in leukemia patients | 24 | 17–90 mCi; intravenous | $^{76}$As as effective as more commonly used leukemia therapeutic agents. |
| BNL | 1950 | $^{131}$I | Determine the usefulness of $^{131}$I to treat patients with Grave's Disease and metastatic carcinoma of the thyroid | 12 | 4–360mCi or 6–20 mCi; route not specified | NA |
| BNL | 1951 | $^{131}$I | Study interaction of the thyroid and $^{131}$I in children with nephrotic syndrome | 8 | NA | Maximum uptake of $^{131}$I was 30-60% of administered dose (3–5 µCi); no impairment of I uptake in children with nephrotic syndrome. |
| BNL | 1952-1953 | $^{42}$K $^{38}$Cl $^{131}$I (1 patient) | Examine formation and cycling of cerebrospinal fluid (CSF) | 2 | NA; injected route not specified | The amount of CSF produced daily is small and fluid production is not solely produced by the choroid plexus |

**Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)**

| Location | Year(s) | Radionuclide | Purpose of experiment | Number of people dosed | Dose and route of exposure | Result |
|---|---|---|---|---|---|---|
| BNL | 1963 | $^{59}$Fe | Study iron absorption in women with various menstrual histories | 9 | 1–10 µCi; oral | Menstrual blood loss in women with excessive bleeding was 110–550 mL. Normal women lost 33–59 mL during menstruation. Heavy menstruating women had higher gastrointestinal tract (GIT) absorption of iron than normal women |
| BNL | 1967 | $^{47}$Ca | Study the role of dietary Ca in osteoporosis | 7 | 25 µCi; intravenous | Diets high in Ca had a small but positive impact on osteoporosis |
| BNL | Early 1970s | $^{82}$Br | Study the kinetics of halothane | 4 | 2.5 µCi; inhalation | Concentrations of halothane were initially high in upper parts of the body and low in lower parts of the body. Diffusion equilibrium throughout the body was achieved in about 24 minutes. |
| HS | 1963 | $^{131}$I | Determine uptake kinetics of $^{131}$I in humans | 8 | NA. Dairy cows consumed 5 mg to 2 g/day of I. Volunteers consumed milk produced by the cows exposed to $^{131}$I in the diet. | Uptake of $^{131}$I in humans was characterized. |
| LBL | 1942-1946 | x ray | Determine if blood cell changes could be used to indicate exposure in workers on the Manhattan Project. | 29 | 5–50 R, daily dose 100–300 R, total dose. Whole body external exposure. | Significant deviations in white blood cell counts, anemia formed in relation to dose. |
| LBL | 1948-1949 | x ray | Determine the effects of radiation on the pituitary gland during treatment of cancers of other tissues | > 1 | 8,000–10,000 rad; external exposure | Pituitary is extremely resistant to x rays. |
| LBL | 1949-1950 | x ray | Effect of radiation on the pituitary gland and its effect on advanced melanoma and breast cancer. | 3 | 8,500–10,000 rad; external exposure | Pituitary is extremely resistant to x rays. |

**Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)**

| Location | Year(s) | Radionuclide | Purpose of experiment | Number of people dosed | Dose and route of exposure | Result |
|---|---|---|---|---|---|---|
| LBL | Early 1950s | $^{60}$Co | Determine feasibility of treating bladder cancer using beads labeled with $^{60}$Co | 35 | 5,000–6,000 rad over 7 days. Beads were placed inside the bladder cavity. | Non-infiltrating cancers were more successfully treated than were the infiltrating bladder cancers. |
| LBL | 1961 | $^{90}$Y | Determine the effectiveness of $^{90}$Y in the treatment of acute leukemia in a child | 1 | 200 rad to lymphatic tissue; route not specified. | Therapy resulted in temporary remission of leukemia; little effect on peripheral blood cells and red blood cells. |
| LLNL | 1980s | $^{13}$N<br>$^{41}$Ar | Determine the uptake and clearance of nitrogen gas in order to better understand “decompression sickness” in deep-sea divers. | 11 | NA. Inhalation route of exposure. Doses in the mCi range.<br><br>Absorbed dose to the lungs estimated to be 0.3–0.5 rad. | NA |
| LANL | 1955 | NA | Obtain information needed to plan for the safe and effective use of military aircraft near “mushroom clouds” during combat operation | 4 | #15 R; Inhalation and external routes were the likely routes of exposure. | No significant internal deposition of fission products or unfissioned Pu were detected in urine or via whole-body counting. |
| LANL | 1961-1962 | $^{85}$Sr | Determine the cutaneous absorption kinetics of $^{85}$Sr through human skin | 2 | 70 µCi; dermal exposure | Absorption of $^{85}$Sr across the skin was low, and ranged from 0.2% to 0.6% total absorption. |
| OR | 1956-1973 | $^{60}$Co<br>$^{137}$Cs | Study efficacy of total-body irradiation on the treatment of leukemia, polycythemia rubra vera, and lymphoma | 194 | 50–300 R, one person received 500 R; external exposure | Higher frequency of remissions after 150 R compared to 250 R. Total body irradiation survived as long-but not longer-than patients treated with non-radiation treatments |
| OR | 1953-1957 | $^{233}$U<br>$^{235}$U | Study the distribution and excretion of uranium in humans | NS. | 4–50 mg; intravenously | 99% of injected uranium cleared the blood within 20 hrs and the remainder either deposited in the skeleton and kidneys or excreted via the urine |

**Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)**

| Location | Year(s) | Radionuclide | Purpose of experiment | Number of people dosed | Dose and route of exposure | Result |
|---|---|---|---|---|---|---|
| OR | 1945 | $^{32}P$ | Study effects of beta rays on skin | 10 | 140–1,180 rad; external exposure. | Threshold dose of beta radiation that resulted in mild tanning was about 200 rad. Erythema resulted after a dose of 813 rad |
| UC | 1937-1954 | x rays | Study the effect of x rays for the treatment of gastric ulcers | 116 | 1,100–2,930 rad; external exposure | Claimed that moderate irradiation of the stomach reduced acid secretion and was a valuable adjunct to conventional gastric ulcer therapy. Therapy was later discontinued due to risks outweighing benefits |
| UC | 1959 | $^{51}Cr$ | Determine feasibility of using implanted radiation sources in the treatment of cancer | 24 | 2–5 mCi; Implanted within cancerous tissues | 16 had good or favorable results; the remainder of patients had questionable or unfavorable results. Implants were generally well tolerated. |
| UC | 1960s | Various. Fallout contains many alpha, beta, and gamma emitting radionuclides. Simulated fallout contained $^{85}Sr$, $^{133}Ba$, or $^{134}Cs$ | Gain information in civil defense planning prior to nuclear fallout | 10 | 0.2–0.7 µCi actual fallout; 0.4–14 µCi simulated fallout. Subjects ingested actual fallout from Nevada test site, as well as simulated fallout particles | No gastrointestinal symptoms were reported. Studies provided a basis for estimating the systemic uptake and internal radiation dose that could result from the ingestion of fallout after nuclear bomb detonation. |
| UR | 1946-1947 | $^{234}U$ $^{235}U$ | Determine dose level at which renal injury is first detectable; measure U elimination and excretion rates | 6 | 6.4–70.9 µCi/kg intravenously | U excretion occurred mainly via the urine and 70–85% was eliminated with 24 hrs. Acidosis decreased U excretion. Humans tolerated U at doses as high as 70 µg/kg |
| UR | 1956 | $^{222}Rn$ | Determine radiation doses to different parts of the respiratory tract from inhaled $^{222}Rn$ | 2 | 0.025 µCi; inhalation | Average retention of $^{222}Rn$ and daughter products in normal atmospheric dust was 25%; retention in filtered air was 75%. Radiation exposure to the lungs was due to radon daughter products rather than by $^{222}Rn$ itself. |

**Table 3-2. Summary of Some Studies of Humans Exposed to Radiation and Radionuclides (continued)**

| Location | Year(s) | Radionuclide | Purpose of experiment | Number of people dosed | Dose and route of exposure | Result |
|---|---|---|---|---|---|---|
| UR | 1966-1967 | $^{212}$Pb | Study absorption of lead from the gastrointestinal tract and determine the radiation hazard and chemical toxicity of ingested lead. | 4 | 1 µCi intravenous and/or 5 µCi orally | Lead might be released from binding sites only when red blood cells die. |
| MISC | 1950s | $^{131}$I | Study the transmission of $^{131}$I in maternal breast milk to nursing infants | 2 | 100 µCi; oral | $^{131}$I concentration in maternal milk was high enough to allow significant uptake in the thyroids of nursing infants. $^{131}$I tracers should be used with caution when nursing infants. |
| MISC | 1953 | $^{131}$I | Study uptake of $^{131}$I by the thyroids of human embryos | NA | 100–200 µCi (maternal dose); route not specified | Pregnant women were scheduled for abortion prior to receiving $^{131}$I. Results indicated that it would be unwise to administer $^{131}$I for diagnostic or therapeutic purposes while pregnant. |
| MISC | 1963-1973 | x rays | Determine the effects of radiation on human testicular function | 60 | 7.5–400 rad; external exposure | Doses of 7.5 rad yielded no adverse effect on testicular function. 27 rad inhibited generation of sperm, and 75 rad destroyed existing sperm cells. Doses of 100–400 rad produced temporary sterility. All persons eventually recovered to pre-exposure levels prior to vasectomy. |

Source: Human Radiation Experiments Associated with the U.S. Department of Energy and its Predecessors. U.S. Department of Energy, Assistant Secretary for Environment, Safety, and Health, Washington, DC, July, 1995. Document #DOE/EH-0491

ANL = Argonne National Laboratory; BNL = Brookhaven National Laboratory; HS = Hanford Sites; LBL = Lawrence Berkeley Laboratory; LLNL = Lawrence Livermore National Laboratory; LANL = Los Alamos National Laboratory; ORS = Oak Ridge Sites; UCLA = University of California, Los Angeles; UCACRH = University of Chicago Argonne Cancer Research Hospital; UR = University of Rochester; MISC = Other miscellaneous studies performed at other institutions; NA = information not available.

hematopoietic manifestations. Similarly, the cells lining the gastrointestinal tract, which normally have high turnover rates, will fail to multiply and replace dying cells, making the body susceptible to malabsorption syndromes, secondary bacterial infections, fluid loss and electrolyte imbalance. Fetal nervous system cells go through a period of rapid development between weeks 8–15, during which time they are more sensitive to radiation damage. Mechanisms by which ionizing radiation affects cells are described in greater detail in Chapter 5 of this profile. The phases of acute toxicity of ionizing radiation are discussed in the following section.

**Acute Radiation Syndrome (ARS).** Doses of radiation below 0.15 Gy (15 rad) produce no observable symptoms or signs. Lifetime radiation exposure from radioactive NPL waste sites, nuclear power plant operations, consumer products, natural background radiation, and most hospital nuclear medical tests are in this range. As the radiation dose increases, subclinical responses begin to occur at 0.15–1 Gy (15–100 rad), and clinical responses occur from 0.5 to $30 Gy (50 to $3,000 rad). Acute radiation syndrome (ARS) is seen in individuals following acute whole body doses of 100 or more rad. The degree of ARS in humans may be classified by the absorbed dose and the time over which the energy from the radiation is deposited in tissue. The clinical phase can be divided into four overlapping phases: (1) a mild phase (0.5–1 Gy, 50–100 rad), (2) hematopoietic syndrome (1–8 Gy, 100–800 rad), (3) the gastrointestinal syndrome (8–30 Gy, 800–3,000 rad), and (4) central nervous system syndrome (>30 Gy, >3,000 rad). If the energy is deposited over more than a few days (i.e., at a lower dose rate), the severity of the effects may be greatly reduced and time of onset delayed. Each of these syndromes and the tissues they are most likely to affect are briefly discussed below.

**Subclinical Response (0.15 to <0.5 Gy, 15 to <50 rad).** This phase is characterized by very few, if any, clinical or hematological manifestations of illness. There are no visible symptoms from this level of radiation exposure. Chromosomal breaks may occur within this dose range. At around 50 rad, there may be transient changes in formed elements of the blood in sensitive individuals.

**Clinical Response (0.5 to $30 Gy, 50 to $3,000 rad).**

***0.5–1 Gy, 50–100 Rad.*** This phase of ARS is characterized by mild, but non-specific signs of toxicity. At 100 rad, most individuals express transient hematopoietic manifestations. Acute clinical signs of toxicity appear within 4–8 hours of receiving the dose; these initially consist of nausea and vomiting. Within 7–15 days after exposure, a moderate leukopenia appears; however, blood cell counts eventually return to normal within 4–6 weeks after exposure. There is no perceptible decrease in mental capabilities. Rest, extra fluids, antibiotics, and self-care are generally all that is needed for these

individuals to fully recover. Any treatment which is offered could include antibiotics and supportive care, much the same as one may treat cold or flu symptoms.

***Hematopoietic Syndrome (1–8 Gy, 100–800 rad).*** This form of ARS is characterized by four phases. The first phase, the prodromal phase, typically lasts up to 2–3 days, depending on the dose; it is characterized by fatigue, listlessness, and lethargy that progresses to headache, anorexia, nausea, and vomiting within approximately 8 hours after initial exposure, depending on the dose. Laboratory findings are limited to varying alterations in the peripheral blood, with the earliest changes demonstrated as a marked lymphopenia about 1 day after exposure. The second stage, the latent phase, begins on the third to fourth day and may last up to 3 weeks from the time of initial exposure. This phase is marked by a progressive decrease in total blood leukocyte counts and hair loss (epilation) toward the third week. The third phase, the symptomatic or bone marrow depression phase, is present 18–21 days after exposure. Chills, fever, malaise, a swollen oropharynx (throat), gingivitis, bleeding gums, petechiae (small blood blisters), ecchymoses (bruises), anemia, and acute infectious diseases are characteristic of persons in this phase. The leukopenia and thrombocytopenia due to destruction of stem cells in the red marrow undermine the body's natural defenses against disease and hemorrhage, leaving the body susceptible to acute infections and illnesses. Depending on the dose and the aggressiveness of the treatment protocols, the clinical picture can vary from serious to fatal. The fourth phase, the recovery phase, is marked by a general improvement of the patient over a 3–6 month period. For doses from 1 to 6 Gy (100 to 600 rad), the prognosis for recovery is good; for doses of 6–8 Gy (600–800 rad) the prognosis is poor, but some victims are expected to survive if they receive aggressive medical treatment. The $LD_{50/30}$ for whole body irradiation is estimated to be between 350 and 450 rad (3.5–4.5 Gy) for those who receive minimal or no medical treatment.

***Gastrointestinal Syndrome (8–30 Gy, 800–3,000 rad).*** The prodromal phase of this syndrome is very abrupt in onset, characterized by nausea and diarrhea, which typically subsides after several days, followed by a short latent period. Symptoms then return, which include white blood cell depression as seen in the hematopoietic form of ARS, nausea, vomiting, diarrhea (sometimes bloody), fever, and massive electrolyte imbalances, which ultimately will result in death. Treatments are palliative. Persons exposed to absorbed doses of $10 Gy (1,000 rad) are expected to die, although aggressive medical intervention may improve survival rates. There is one exception. If the dose is fractionated, as with bone marrow transplant patients who receive a standard whole body dose of 15.75 Gy (1,575 rad) and are well-managed, with fluids, antibiotics, and a sterile environment, the individual has a reasonable chance of survival.

***Central Nervous System Syndrome (≥30 Gy, 3,000 rad).*** Symptoms in this syndrome classically have an immediate onset, and include violent nausea and vomiting, diarrhea, irrational behavior, circulatory system collapse, and neuromuscular incoordination occurring within a few minutes after irradiation. Convulsions, coma, and death ensue within 48 hours after irradiation.

The phases of acute radiation effects discussed above are summarized in Table 3-3.

**Studies of Acute Effects.** Most studies which showed acute radiation effects were from external radiation, indicating that internally-deposited radionuclides typically do not produce sufficient dose and dose rate to induce acute effects. As Table 3-3 shows, the overt signs of radiation toxicity follow a dose-effect relationship as long as the radiation dose rate is high. Individuals exposed to single acute doses of radiation that are less than 1 Gy (100 rad) experience few if any significant clinical signs of toxicity; however, as the dose is doubled (2 Gy, 200 rad), some systems begin to show signs of overt toxicity. At this dose, the cells that multiply the most rapidly (gastrointestinal cells, blood-forming cells) are only being mildly affected (nausea/vomiting, leukopenia). Red blood cell precursors are also likely to be affected at this dose; however, because of the lifespan of a peripheral red blood cell (90–120 days), anemia may not become clinically evident for several days or weeks after exposure. Cells that proliferate more slowly (e.g., the cells of the central nervous system, connective tissues, etc.) are largely unaffected. As the absorbed dose increases to 6 Gy (600 rad), more severe changes in the hematopoietic and gastrointestinal systems present as more intense, quicker onset vomiting for longer durations and severe white blood cell depression (leukopenia). Infections are of a greater concern, since the white blood cell's main defenses against infectious microorganisms (gastrointestinal cell barriers, neutrophils, lymphocytes) are severely compromised or non-functional. Coagulapathies begin to appear due to platelet anomalies (pupura, hemorrhage) as well as hair follicle death (hair epilation). Also at this dose, the first signs of central nervous system disruption begin to appear, with short periods of decreased cognitive abilities. As the dose of ionizing radiation increases beyond 8 Gy (800 rad), a dose-dependent increase in the severity of the hematological, gastrointestinal, and central nervous system toxicity occurs, and death will likely ensue due to catastrophic multi-organ failure, including complete destruction of the blood forming cells in the red marrow and destruction of the basement cells in the lining of the intestinal walls.

## Table 3-3. Summary of the Dose Response Effects of Ionizing Radiation in Humans

| Phase | Feature | Subclinical range | 100–800 rad (sublethal ranges) | | | Over 800 rad (lethal range) | |
|---|---|---|---|---|---|---|---|
| | | 0–100 rad | 100–200 rad | 200–600 rad | 600–800 rad | 800–3000 rad | >3000 rad |
| Initial phase | Incidence of nausea and vomiting | None | 5–50% | 50–100% | 75–100% | 90-100% | 100% |
| | Time of onset | | 3–6 hours | 2–4 hours | 1–2 hours | <1 hr | < 1 hr |
| | Duration | | <24 hours | <24 hours | <48 hours | <48 hours | 48 hours |
| | Mental and physical capabilities | 100% | 100% | Able to perform routine tasks. Cognitive abilities impaired for 6–20 hours. | Able to perform simple and routine tasks. Significant incapacitation in upper part of dose range. Lasts more than 24 hours. | Progressive incapacitation | |
| Latent phase | Duration | > 2 weeks | 7–15 days | 0–7 days | 0–2 days | None | |
| Secondary phase | Signs and symptoms | None | Moderate leukopenia | Severe leukopenia; pneumonia; purpura, hemorrhage; infection; hair loss (epilation) at about 300 rads | | Diarrhea; fever; disturbance of electolyte balance | Convulsions; tremor; ataxia; lethargy |
| | Time of onset after exposure | | >2 weeks | Several days to 2 weeks | | 2–3 days | |
| | Critical period after exposure | | None | 4–6 weeks | | 5–14 days | 1–48 hours |
| | Organ system affected | None | | Hematopoietic and respiratory tissues | Hematopoietic and respiratory tissues | Gastrointestinal tract;respiratory tissues | Central nervous system |
| Hospitalization | Percentage | None | <5% | 90% | 100% | 100% | 100% |
| | Duration | | 45–60 days | 60–90 days | 90–120 days | 2 weeks | 2 days |
| Incidence of death | | None | None | 0–80% | 90–100% | 90–100% | |
| Average time to death | | | | 3 weeks to 2 months | | 1–2 weeks | 2 days |
| Medical therapy | | None | Hematologic surveillance | Blood transfusions and antibiotics | | Maintenance of electrolytebalance | Sedatives |

Source: adapted from Academy of Health and Science 1995

Death has been reported soon after an individual has received a very high single or multiple external radiation dose. Most of these studies have in common very high doses (several hundred to several thousands of rad) being administered over a relatively short period of time (acute exposure), usually over the course of minutes or hours. This was seen in the human case report by Stavem et al. (1985) in which a worker was exposed to 2,250 rad (22.5 Gy) within a few minutes time, resulting in death due to acute radiation sickness (depressed leukocyte counts, vomiting, diarrhea, etc).

There are many reports of studies in which animals inhaled large activities of soluble and insoluble particles. The inhalation studies pointed to a number of immediate or near-immediate causes of death, including bone marrow hypoplasia (Gillette et al. 1987a); radiation pneumonitis and fibrosis (Brooks et al. 1992; Hahn et al. 1981, 1987; Lundgren et al. 1991); and blood abnormalities, such as thrombocytopenia, neutropenia, lymphopenia, and anemia (McClellan et al. 1973). Death is most likely a result of these systems being adversely affected by the deleterious effects that radiation has on the cell functionality within these organ systems. The overwhelming damage that radiation induces in rapidly dividing (or undifferentiated) cells at these high doses (i.e., cell functional loss, necrosis, apoptosis, and death of precursor cells) leads to decreased numbers of functional cells for an extended period of time, leaving the body highly susceptible to systemic infections that can lead to organ failure and death. It has been suggested that the damage to lung tissue from radiation is principally vascular, with the sloughing of dead and dying endothelial cells causing capillary leakage, both interstitially and onto the alveolar surface. Another theory suggests that the damage to type II pneumocytes causes serious alterations in the amount of surfactant phospholipids, ultimately altering the normal functioning of the lung and leading to lung inflammation. A third theory suggests that type I pneumocytes necrose and slough, leaving denuded basement membranes and alveolar debris. Finally, a few researchers believe that the role of lymphocytes, the immune system, and the interaction of bacteria plays a major part in the induction of radiation pneumonitis (Coggle et al. 1986). In the case of experimental animals given acute doses, causes of later in life are primarily related to the cancerous effects (Boecker et al. 1988; Lloyd et al. 1994).

The clinical signs of toxicity from high radiation doses follow the classic dose-effect curve, with some organs more severely affected at each dose than others. A number of studies have been summarized that describe the no-observed-adverse-effect level (NOAEL) and the lowest-observed-adverse-effect level (LOAEL) of ionizing radiation on multiple body systems. These data are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile. More specific information on some organ systems affected after receiving high doses of ionizing radiation is discussed in more detail below.

#### 3.2.1.1 Gastrointestinal Effects

Prominent gastrointestinal effects due to high acute doses of radiation can occur, usually after oral intakes of radionuclides or after whole-body exposures. Localized doses of external radiation of about 1,000 rad (10 Gy), have been reported to cause inflammation and swelling of the oral cavity, including the cheeks, soft and hard palate, tongue, and throat. The large doses necessary to cause these effects and the absence of effects following dental x rays demonstrate that salivary glands are not very sensitive to radiation. The structures near the stomach, which have stratified squamous epithelial coverings, seem to be much less severely affected than the stomach, small and large intestines, and colon, largely due to the lower cell turnover rates associated with this type of epithelium. The gastrointestinal epithelium, which includes the epithelium covering the stomach and intestines, is the most sensitive to the effects of radiation due to the high cell turnover rates. Very large doses (>1,000 rad, 10 Gy) to the germinal epithelium of the stomach and intestines damage these cells, rendering them unable to divide and replace older, more senescent cells lining these structures. As a result, ulceration, sloughing of cells, diarrhea, and hemorrhage may occur, leading to the gastrointestinal syndrome described in Table 3-3 (Adams and Wilson 1993).

Numerous laboratory animal studies identified gastrointestinal effects after exposure to high-level radiation. For example, male Swiss albino mice were injected with tritiated water with a specific activity of 10 mCi/mL, followed by maintenance on tritiated drinking water at 2.5 μCi/mL for 12 days. Mice were estimated to have cumulative doses of 116, 440, 1,320, 2,200, and 5,280 mrad (1.2, 4.4, 13.22, and 5.3 mGy) for the 0.25, 1, 3, 5, and 12 days of treatment, respectively. A significant decrease in the total cell population and mitotic figure per crypt section was observed 6 hours after exposure; the decrease continued through day 1. After that, the total cell population stayed at a constant value for 3–5 days), after which it showed a significant increase on day 12. The number of mitotic figures increased slightly on day 3 followed by a decrease on day 5, but these changes were not significant. On day 12, the mitosis also increased slightly. The number of pycnotic nuclei and necrotic cells increased significantly 6 and 24 hours after exposure, and then decreased on day 3. After that, the number of cells increased again on day 5. The number of cells per villus column showed a significant decrease 6 hours after exposure; this decline continued up to day 5, when the cell count was 67.5% of normal (control). After this, the count showed a significant increase on day 12. The villus height was slightly reduced 6 hours after exposure, and significantly reduced from day 1 to 5. The height was 81% of normal at day 5, and 91.5% of normal at day 12. In summary, all of the parameters studied showed partial recovery towards normal on day 12 at the doses tested (Kumar et al. 1983).

Gastrointestinal effects have also been described after inhalation exposure to radionuclides. Gastrointestinal effects are most likely due to inhaled particles lodging in the nasopharyngeal mucus and in the tracheobronchial mucus layers of the conducting airways of the lungs and then being carried up the airways, where they enter the pharynx and are swallowed. Several reports describe such gastrointestinal effects after inhalation exposure. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) once to soluble aerosols containing $^{90}SrCl_2$. Different airborne concentrations (2.16–418.5 μCi $^{90}Sr$/L) and exposure durations (2–22 minutes) were used to produce graded levels of initial lung burdens; 72 Beagle dogs were exposed, and another 25 unexposed dogs served as controls. The long-term retained burden ranged from 1.0 to 118.8 μCi $^{90}Sr$/kg body weight. Clinical signs of radiation-induced illness appeared about 2 weeks after exposure. The first signs, fever and anorexia, including bloody diarrhea, developed during the last 48 hours before death. In another study, Hahn et al. (1975) studied the effects of $^{90}Y$ laden particles clearing to the gastrointestinal tract after an acute-duration inhalation exposure. Ten Beagle dogs were exposed by nose-only inhalation to aerosols of $^{90}Y$ in fused-clay particles; three control dogs were exposed to fused clay only. Gastrointestinal burdens ranged from 8 to 34 mCi. A rapid initial decrease in body burden occurred (typical of an insoluble material deposited by inhalation), which was largely due to the clearance of particles from the upper respiratory tract through the gastrointestinal tract by way of mucociliary clearance mechanisms in the respiratory tract; 4 of 6 dogs with 18–34 mCi gastrointestinal burden developed a mucoid diarrhea. The dog with the highest exposure developed hemorrhagic diarrhea; 2 of 7 dogs exposed to 18–32 mCi gastrointestinal tract burden (32–50 mCi whole-body burden) developed colitis. At necropsy, lesions were found to be confined to the colon, except for one dog with ulcerative esophagitis. No gross lesions were seen in the stomachs or small intestines of any of the dogs; no histologic lesions were found. In the dogs with colitis, ulcerative and atrophic foci were scattered in the terminal third of the colon. Loss of mucosal epithelial cells and collapse of the lamina propria were the most severe pathologic alterations in the colon. The colon received the highest radiation dose in the two exposed dogs, although the stomach and small intestines also received significant doses. Of the two dogs sacrificed at 8 days postexposure, the only lesions that were seen at necropsy were in the colon of the dog that received an estimated 3,200–5,700 rad (32–57 Gy). No lesions were seen in the intestines of the dog that received 2,800 rad or less. Lesions were most likely in response to a high dose of ionizing radiation due to the long transit time of the radiolabeled material through the colon (increased exposure time).

Similar effects from external gamma radiation have been reported. In one human case report, Stavem et al. (1985) described a 64-year-old male worker who accidentally received a large dose of gamma radiation in a plant for sterilizing medical equipment. He was exposed for only a few minutes and was

most likely exposed to a mean whole-body dose of 2,250 rad. The worker developed ARS. Histologically, the mucosa of the gastrointestinal tract (and respiratory tract) showed only a few mononuclear cells, and no granulocytes. There was slight atrophy of glands in the stomach, marked atrophy in the small intestine, and total atrophy of the glands in the large intestine. As in humans, laboratory animals exposed to extreme doses of external radiation exhibit effects on the exposed organ systems. A group of 12 male BALB/c mice was exposed to a single whole-body dose of 1,500 rad gamma rays from a $^{60}$Co source. The degree of gastrointestinal motility and the condition of the abdominal blood vessels, spleen, and the contents of the stomach and intestine were examined 1 hour, 3 hours, 18 hours, and 3 days after irradiation. Gastrointestinal mobility was present at all times after the exposure. Vascular dilatation was absent at all times. Lumial contents were present 1–3 hours after the exposure and slightly present 18 hours to 3 days after the exposure. The mucosal surface displayed changes in the shape of the villi, with rudimentary villi being the most advanced type of collapse seen. Villus shape changes were seen at all times post-exposure. Changes in tissue structure were seen at the 18-hour time point including less distinct crypts with disintegrating cells present (Indran et al. 1991). Ijiri (1989), studying the influence of circadian rhythm on apoptosis, found that gamma irradiation (from $^{137}$Cs) between 0900 and 1500 hours caused a higher incidence of apoptotic cells in the small intestine of male C57BL/6crSlc mice than irradiation between 2100 and 0300 hours, irrespective of dose rate; similar differences, but with lower incidences of apoptotic cells, were also noted in the descending colon. The mean lethal dose values for continuous irradiation with gamma rays were 21 rad (0.21 Gy) for the cells of the small intestine and 38 rad (0.38 Gy) for the cells of the descending colon, and the respective values for HTO (beta radiation) were 13 and 28 rad (0.13 and 0.28 Gy), indicating the high radiosensitivity of these cells.

In summary, higher doses, starting in the range of 200–300 rad (2–3 Gy), are required to produce effects in the gastrointestinal tract than in bone marrow. The severity of effects follows a typical dose-effect relationship. The cells responsible for lining the tract frequently undergo mitosis, leaving them particularly susceptible to DNA damage, cell death, and altered cell kinetics that affect the cell's ability to proliferate. These effects include karyorrhexis (fragmentation of a nucleus with scattering of pieces in the cytoplasm), pyknotic nuclei (having polymerized and contracted chromosomal components), necrosis, decreased number of cells/villi, and changes in shapes of the villi and mucosal surfaces. The damage to the epithelial lining cells results in the loss of the natural barrier between intestinal microbes and the body, making it susceptible to systemic infections, fluid imbalances and losses, bloody diarrhea, colitis, and a host of other clinical signs, depending on the radiation dose (Gillett et al. 1987a; Hahn et al. 1975; Kumar et al. 1983).

Data for acute gastrointestinal effects in humans and laboratory animals from large doses of radiation are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

#### 3.2.1.2 Hematological and Lymphoreticular Effects

Hematological effects are one of the syndromes seen after acute doses to bone marrow (see Table 3-3) of about 50 rad (0.5 Gy). The magnitude of effect on hematopoiesis is dependent on the total dose absorbed, regardless of the route of exposure. As Table 3-3 shows, hematological symptoms begin to occur at doses of 100–200 rad (1–2 Gy). Like the gastrointestinal system, the hematopoietic system contains a large population of cells that requires the frequent replacement of senescent cells. To meet this need, a pool of undifferentiated precursor cells called stem cells in the red marrow of many bones (e.g., ribs, pelvis, vertebrae, skull, and ends of long bones) undergo high rates of mitotic activity and differentiate into the various cell types to replace those that die off naturally. This pool of cells is critical for the production of replacement cell populations for erythrocytes, granulocytes, lymphocytes, and thrombocytes. The dose of radiation received by stem cells damages or kills these cells, thereby depressing the marrow activity, resulting in anemia, leukopenia, thrombocytopenia, septicemia, infections, and death. The severity of these lesions depends on the depression of bone marrow activity due to the total dose absorbed, with irreversible total destruction resulting from doses to the red marrow on the order of 800 or more rad ($8 Gy).

As an example of hematological lesions in humans obtained after exposure to ionizing radiation, Klener et al. (1986) reports one case in which a man was accidentally irradiated by a sealed $^{60}$Co source. His health status was followed for 11 years after the accident. A film dosimeter worn during the accident indicated an exposure of 159 rad (1.59 Gy). Twelve to 24 hours after the accident, the worker felt general malaise without vomiting; however, a blood count showed no marked deviations from normal. Eight days after the accident, he developed minor deviations in peripheral blood counts. Leukocyte values were lowest 31–49 days after exposure. The lymphocyte count was normal the first day after the accident, but decreased on days 19–23 and day 49. Neutrophils with coarse granulations and hypersegmentation of nuclei were observed. In another acute exposure case, Stavem et al. (1985) reported on a 64-year-old male worker who was accidentally exposed to gamma radiation in a plant that used ionizing radiation for sterilization purposes. He was exposed for only a few minutes and received an estimated 2,250 rad (22.5 Gy). The worker developed ARS, with the leukocyte count rapidly diminished to low values. Extensive chromosome injuries were seen in cultured blood lymphocytes, and virtually no undamaged

cells were found. The worker died 13 days after exposure. An autopsy found the bone marrow to be markedly hypocellular with a few scattered plasma cells.

Hematological effects have been reported after inhalation exposures in laboratory animals. The effects depend on the dose absorbed. Brooks et al. (1992) exposed male monkeys, divided into mature (5.0±0.5 kg) and immature (2.1±0.3 kg) groups, to an aerosol of $^{239}Pu(NO_3)_4$ by nose-only inhalation to produce projected initial lung burdens of either 1.08, 0.27, or 0.1 µCi (40, 10, or 3.7 kBq). No significant changes in blood lymphocyte numbers were observed. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) to soluble aerosols containing $^{90}SrCl_2$. A review of the hematological parameters of all dogs showed a similar, consistent, and dose-related pancytopenia in those animals having a long-term retained burden greater than 10 µCi (370 kBq) $^{90}Sr$/kg. A profound dose-related depression of platelet counts was also found. Decreases in platelet numbers were manifested by 7 days and were maximal by 28 days. Platelet counts were depressed in all exposed groups, compared to controls, when evaluation was extended to 1,000 days after exposure. Platelet counts among animals having a long-term retained burden greater than 40.5 µCi (1,500 kBq) $^{90}Sr$/kg frequently fell to less than 10% of pre-exposure values. Animals having slightly lower long-term retained burden also exhibited depressed but less severe thrombocytopenia. The degree of platelet depression was related to the degree of long-term retained $^{90}Sr$. The decline in platelet counts seen in dogs with a long-term retained burden of 27.0–118.8 µCi $^{90}Sr$/kg at 1,000 days was also associated with the presence of hemangiosarcomas. Thrombocytopenia and neutropenia persisted in all exposed dogs through 1,000 days after exposure. Lymphocyte numbers were also depressed in a dose-related manner at activity concentrations greater than 10 µCi (370 kBq) $^{90}Sr$/kg. Reduced erythrocyte mass occurred in dogs having a long-term retained burden greater than 10 µCi (370 kBq) $^{90}Sr$/kg between 14 and 21 days after exposure. Red blood cell counts fell to 70–80% of pre-exposure values, with maximal depression at 32 days.

Hobbs et al. (1972) also observed dose-related clinical, hematological, serum chemical, and pathological alterations more than 1 year after intake. Thirty-three Beagle dogs were given lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, 110 and 0 µCi (133, 67, 44, 29, 15.8, and 4 MBq) $^{90}Y$/kg body weight. Cumulative doses between 990 and 55,000 rad (9.9–550 Gy) to the lungs through the end of the study or the death of the animals were reported. Dogs that had initial lung burdens of 670–760 µCi/kg (25–28 MBq) and radiation doses to lung of 8,400 to 9,400 rad (8.4–9.4 Gy) and died within 31 days after intake had a dose-related depression of circulating lymphocytes (lymphopenia), as well as a marked

marrow suppression and deletion of hemic elements. Rib marrow was depopulated in dogs that died after 31 days.

Exposure to primarily β and γ radiation from external sources yielded similar results. Seed et al. (1989) exposed male and female Beagle dogs to 7.5 rad/day (0.075 Gy/day) gamma radiation for 150–300 days from a $^{60}$Co source. The irradiated dogs showed a significant suppression/recovery pattern for the five circulating types of cells studied (granulocytes, monocytes, platelets, erythrocytes, and lymphocytes), compared with levels from the control animals. These daily doses were high and would have likely been fatal if the entire dose had been received within a period of a few days.

A large number of reports are available in the literature regarding immunological effects associated with radionuclides that have been inhaled by laboratory animals. Lymphopenia is a common sequela of exposure to ionizing radiation affecting the immune system of both humans and animals. Gillett et al. (1987a) exposed young adult Beagle dogs (12–14 months old) to soluble aerosols containing $^{90}SrCl_2$ and found that lymphocyte numbers were depressed in a dose-related manner at exposures greater than 10 μCi $^{90}$Sr/kg. Benjamin et al. (1976) exposed 6 Beagle dogs, (3 males and 3 females, 17–20 months old) by nose-only inhalation to $^{90}$Y, $^{144}$Ce, or $^{90}$Sr in fused-clay particles. Initial lung burdens were 560, 46, and 28 μCi/kg (21, 1.7, and 1.0 MBq/kg) for $^{90}$Y, $^{144}$Ce, and $^{90}$Sr, respectively. Cumulative absorbed dose at death or at sacrifice after 44 weeks were 8,700, 42,000, and 39,000 rad (87, 420, and 390 Gy) for $^{90}$Y, $^{144}$Ce, and $^{90}$Sr exposures, respectively. Lymphopenia was observed in dogs exposed to $^{90}$Y within several days after intake and was statistically significantly depressed though 8 weeks but returned to control levels by 16–20 weeks. No change in peripheral lymphocytes was observed. Lymphocyte counts in dogs exposed to $^{144}$Ce were significantly lower (lymphopenia) than controls from 4 to 28 weeks after exposure. In a study conducted by Lundgren et al. (1976), the effect of $^{90}$Y inhaled in fused-clay particles on the pulmonary clearance of inhaled *Staphyloccus aureus* in mice was investigated. Groups of male CFW mice were exposed to $^{90}$Y for 10–20 minutes. Aerosol concentrations ranged from 14.5 to 428 μCi/L (0.5–16 MBq/L) air and the activity median aerodynamic diameter (AMAD) ranged from 0.7 to 1.4 μm. The initial lung burden ranges of the groups were 2.5–4, 7–12, 20–47, and 50–76 μCi in experiment I and 5–7 and 8–12 μCi in experiment II. Pulmonary clearance of inhaled *S. aureus* was suppressed in mice with an initial lung burdens of 20 μCi $^{90}$Y or greater at 2, 3, and 4 weeks after exposure. Lymphocyte counts were suppressed in the 20–47 μCi and 50–76 μCi groups at 2 weeks postexposure and in the 50–76 μCi group at 3 weeks after intake. Clearance of bacteria at a reduced rate was observed in 20–47 μCi mice at 2, 3, and 4 weeks and in 50–76 μCi mice at 2 and 3 weeks after intake.

Similarly, Hobbs et al. (1972) observed dose-related pathological alterations more than 1 year post-exposure in 33 Beagle dogs exposed to $^{90}Y$. Of the 33 dogs exposed, 21 with initial lung burdens from 670 to 5,200 μCi/kg (25–192 MBq/kg) and radiation doses to the lungs ranging from 8,400 to 55,000 rad (84–550 Gy) died between 7.5 and 163 days after intake. Tracheobronchial lymph nodes (TBLNs) in the early deaths showed marked lymphoid depletion, some sinus hemorrhage, and, later, phagocytosis of hemosiderin pigment. In the dogs that died 38 days or more postexposure, the nodes were enlarged and exhibited hyperplastic repopulation of lymphocytes. Hahn et al. (1976) also studied the effects of exposure on TBLNs in 16 male and 14 female Beagle dogs exposed by nose-only inhalation to aerosols of $^{144}Ce$ in fused-clay particles. Between 2 and 730 days postinhalation, the $^{144}Ce$ dose to TBLNs ranged from 240 to 230,000 rad (2.4–2,300 Gy). The concentration of $^{144}Ce$ in the TBLNs increased during the first year after exposure as a result of the translocation of $^{144}Ce$ from the lungs via the lymphatics. Histologically, the changes were atrophic in nature. The cortex showed progressive reduction in size with increasing time after intake; by 730 days after intake, there was little cortex remaining. Fibrosis was first noted 128 days after intake and was more severe at each succeeding time period up to 730 days. There was also a loss in numbers of lymphocytes in the paracortical area 56 days after intake, although this loss was not as severe as the depletion of lymphocytes from the cortex. At later times the cortical and paracortical areas were nearly devoid of lymphocytes and were populated mainly by macrophages. Particles could be seen in macrophages 2 days after inhalation exposure. The authors note that since lymph nodes play a key role in immunologic responses associated with humoral antibody production and cell-mediated immunity and, in view of the severe atrophy and fibrosis in the TBLNs in the dogs in this study, the immunologic function in the TBLNs would seem to have been severely impaired.

Lymphocytes are responsible for providing cell-mediated and humoral-mediated (antibodies) resistance to infection. Galvin et al. (1989) evaluated the cell-mediated and humoral immune responses to $^{239}PuO_2$ in the blood and lung lavage fluid. Four Beagle dogs per group (8 total) were exposed to monodisperse aerosols (0.72–1.4 μm AMAD) of $^{239}PuO_2$, with initial lung burdens ranging from 0.51 to 0.95 μCi (0.02–0.04 MBq). Cumulative dose ranges were 1,400–2,400 rad (14–24 Gy) to the lungs; 620,000–930,000 rad (6,200–9,300 Gy) to the TBLNs; 290,000–440,000 rad (2,900–4,400 Gy) to the mediastinal lymph nodes; 200–300 rad to (2–3 Gy) the sternal lymph nodes; and 2–3 rad (0.02–0.03 Gy) to the spleen. The dog with the highest cumulative dose to the TBLNs (930,000 rad, 9,300 Gy) was the only dog noted to have had chronic lymphopenia; blood cell counts of the other 3 dogs showed normal lymphocyte counts. TBLNs of all dogs displayed severe diffuse fibrosis and atrophy with elimination of all lymphatic cells and follicles. Lymphatic vessels were moderately to markedly distended. The spleen

and other peripheral lymph nodes were histologically normal. Systemic humoral response induced by lung immunization was not different in the age-matched and exposed groups. Peak humoral immune response (lung lavage, immunoglobulin G [IgG]) measured in immunized lung lobes of exposed and control dogs was significantly greater than saline-lavaged control lung lobes.

Leukopenia (severe lymphopenia and granulocytopenia) and splenic congestion were found in one male worker who accidentally received an external gamma dose of 2,250 rad (22.5 Gy) (Stavem et al. 1985). Mazur et al. (1991) exposed male Swiss mice to a single dose of 1,000 rad (10 Gy) whole-body irradiation from a $^{60}$Co source. Spleen weights were significantly lower in the irradiated group during the 24-hour period. No statistically significant differences in acid phosphatase activity were seen in the spleens and livers of radiation-exposed mice; however, the acid phosphatase activity in the spleen and liver was statistically significantly higher in the irradiated rats as compared to controls. An increased activity of beta-glucuronidase was seen in the spleen, but the enzyme activity did not differ from controls in the liver.

In summary, the hematological and lymphoreticular systems are target systems susceptible to the effects of ionizing radiation, the severity of which occurs in a dose-dependent manner. As with the gastrointestinal tract, the hemopoietic system is largely composed of undifferentiated rapidly dividing cells, making it more susceptible to the toxic effects of ionizing radiation than are the tissues composed of highly differentiated more slowly dividing cells (central nervous system). In many of the studies, pancytopenia was one of the first major peripheral blood changes to occur. Neutrophils have a naturally short lifespan in the peripheral blood (12–48 hours) and depend upon constant replenishment by the bone marrow to adequately defend the body against infection. Acute high (sublethal) radiation doses from an external source or from inhaled or ingested radionuclides that distribute to bone and irradiate the sensitive cells in the bone marrow will first noticeably affect the progenitor cells that produce leucocytes, since their turnover rates for this cell type are very high. The immediate peripheral blood counts of red blood cells with longer lifespans in the peripheral blood and lower turnover rates will not be affected because of their long lifetime (3–4 months). Radionuclides that preferentially distribute to the bone for long periods of time will, if the dose is high, cause prolonged depression of most red and white blood cell types, due to constant irradiation of the bone marrow components. Anemias, thrombocytopenia, and leukopenias (all cell types) are also frequent findings in such situations (Benjamin et al. 1976, 1979; Davila et al. 1992; Gillette et al. 1987a; Hahn et al. 1976; Hobbs et al. 1972). Animals administered sublethal doses of ionizing radiation have the ability to recover from these effects once the radiation source is removed (Gidali et al. 1985; Hobbs et al. 1972; Seed et al. 1989, 1993) or its dose rate is sufficiently reduced.

The data for hematological and lymphoreticular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile. Because of the high threshold dose for changes in peripheral blood counts, blood counts are not used to routinely monitor the health of radiation workers.

#### 3.2.1.3 Reproductive Effects

Cells that reproduce frequently, such as those found in intestinal crypts, bone marrow, and the reproductive systems of animals, are more radiosensitive than cells that are highly differentiated and reproduce slowly. This radiosensitivity is dependent on of the type of ionizing radiation or the source. Specific cells in the reproductive tract of both males and females replicate at accelerated rates, making them more at risk to the effects of ionizing radiation. In males, the spermatogonia are the cells most sensitive to the effects of ionizing radiation. These are the germ cells responsible for producing spermatocytes and later, spermatids and mature sperm. Spermatids and sperm are very radioresistant to cytotoxic effects of radiation. Decreases in sperm numbers in semen do not occur immediately; in humans, decreased sperm counts are not seen until 30–45 days after significant exposures. Azospermia can occur 10 weeks after exposure to absorbed doses >100 rad (1 Gy); a dose of 250 rad (2.5 Gy) may cause sterility for 1–2 years. An absorbed dose of 600 rad (6 Gy) can cause permanent sterility (Adams and Wilson 1993). In females, the mature oocyte is less sensitive than male spermatogonia cells, but it is the most radiosensitive reproductive cell. Absorbed doses of 65–150 rad (0.65–1.5 Gy) have been reported to produce temporary sterility (Adams and Wilson 1993); however, a fractionated dose of 600–2,000 rad (6–20 Gy) can be tolerated (BEIR V 1990).

Several studies were found in the literature that support these findings. In one human study, Birioukov et al. (1993) investigated the reproductive effects of ionizing radiation in 12 men (29–78 years old) with chronic radiation dermatitis caused by accidental exposure to beta and gamma radiation during and after the Chernobyl nuclear reactor accident. These men were examined for changes in sexual behavior, hormonal status, and spermatogenesis. All were diagnosed with ARS, which was categorized as first degree (100–200 rad, 1–2 Gy), second degree (200–350 rad, 2–3.5 Gy, Group A), and third degree (350–550 rad, 3.5–5.5 Gy, Group B) based on their location at the time of the incident. Of the 12 men evaluated, 9 reported decreased sexual potency, and 3 refused to answer the question. Two patients reported impotence, and seven patients had decreased libido. The sperm of 7 patients were examined (5 refused to give a semen sample). All patients tested had normal semen pH values. Other sperm

anomalies reported in both groups A and B included azoospermia, asthenospermia, and teratospermia. Others had slightly increased numbers of abnormal cells (morphological changes in the sperm head). Abnormal motility was present in all but one patient (in group B). Follicle-stimulating hormone was increased in 6 of 9 patients in group A and was normal in group B patients. Testosterone was decreased in 2 patients in each group. A decrease of luteinizing hormone and an increase of prolactin were measured only in 1 patient.

Similar reproductive effects have been noted in laboratory animals. Ramaiya et al. (1994) performed a comparative estimation of the frequencies of genetic disorders induced in germ cells of male mice by a single or long-term exposure to incorporated $^{137}$Cs. Groups of 10 male mice received a single oral administration of 0.1, 0.5, 1.0, 2.0, and 3.0 µCi/g (3.7, 18, 37, 74, and 111 kBq/g) as $^{137}$Cs. Groups of 10–30 males were also given daily injections of $^{137}$Cs nitrate in phosphate buffer solution for 2 weeks at activities of 0.5, 2.0, and 5.0 µCi/g (18, 74, and 190 kBq/g) as $^{137}$Cs. The total absorbed dose to the testes during the 5 weeks after the single oral exposure was 10, 50, 100, 200, and 300 rad (0.1, 0.5, 1.2, and 3 Gy), respectively, while the total absorbed doses during the 5 weeks of multiple injections was 38, 154, and 385 rad (0.38, 1.54, and 3.85 Gy), respectively. A decrease in the fertility of males was observed in the 2.0 and 3.0 µCi/g (74 and 111 kBq) exposure groups, beginning from the 4th week for radiation doses of 190–197 rad and 285–295 rad (1.90–1.97 Gy and 2.85–2.95 Gy), respectively. Complete, but temporary, sterility observed in animals exposed to 300 rad (3 Gy) after 6 weeks was attributed to the death of spermatogonial cells. There was a significant increase in post-implantation embryo mortality and, correspondingly, in the dominant lethal mutation frequency, at a total dose of $180 rad (1.8 Gy).

Pinon-Lataillade et al. (1991) irradiated male Sprague-Dawley rats so that only the testes and surrounding organs were exposed to a gamma-ray beam of 900 rad (9 Gy). Groups of 6 irradiated rats and age-matched controls were sacrificed at 7, 15, 23, 34, 50, 71, 118, and 180 days after irradiation. Testis weight dropped to 85% of the control by day 7, 58% of the control by day 23, and 41% by day 34. Epididymal weight decreased to 88% of control by day 15, 63% by day 50, and plateaued out at 55% of the control value. Spermatocytes were damaged, and by day 34, only elongated spermatids remained in a few tubules and very little regeneration of the seminiferous tubule had occurred. From day 15 after the irradiation, the epididymal content of androgen-binding protein (ABP) value dropped to 26% of the control and by day 34 it was back to only 14% of this value. From day 50 to the end, the ABP value remained below 10% of the control levels. No significant changes were observed in the weights of the seminal vesicles or in the concentrations of seminal vesicles.

Another study of acute duration estimated comparative frequencies of genetic disorders induced in germ cells of male mice by a single or long-term exposure to incorporated $^{137}$Cs or to external gamma radiation. Groups of 10 male mice were exposed to a $^{137}$Cs apparatus for a whole-body dose of gamma radiation of 300 rad (3 Gy) at a rate of 0.675 rad/hour. Subsequent data on effective matings and embryo mortality were collected. Animals that mated and that were exposed to external gamma radiation had a significant decrease in male fertility, and at 3 weeks the animals became sterile. During weeks 1 and 2, there was a significant increase in total and post-implantation embryo mortality (Ramaiya et al. 1994).

Studies of longer exposure duration have demonstrated similar results. Searle et al. (1976) exposed 13 adult C3Hx101 hybrid male mice continuously to 1,128 rad (11.28 Gy) $^{60}$Co gamma radiation over 28 weeks at the rate of 5.8 rad/day (0.058 Gy/day). There were significant reductions in testis mass (35% of controls) and epididymal sperm count (15% of controls). An increased percentage of abnormal sperm was observed in gamma-irradiated animals (17.1% versus 3.9% controls). The frequency of chromosomal translocations was significantly higher than in controls. There was also good evidence for the induction of dominant lethal mutations, with an increase in pre-implantation loss from 16% (controls) to 28% (radiation exposed) and in post-implantation loss from 10% (control) to 22% (radiation exposed). In addition, Grahn and Carnes (1988) exposed groups of 4–13 male B6CF$_1$ mice to $^{60}$Co gamma-rays or fission neutrons at once-weekly doses for periods up to 60 weeks (10, 25, 40, 50, or 60 weeks of exposure and observations at 75, 90, and 99 weeks). Doses rates were 0, 5, 7.5, and 10 rad (0, 50, 75, and 100 mSv) per week. An increased frequency of abnormal sperm was observed at all doses and all exposure durations. After exposure ended, frequencies of sperm abnormalities returned to near-normal levels.

In summary, male reproductive organs are at risk for non-carcinogenic effects when exposed to high doses of ionizing radiation due to the relative high rates of cell divisions that occur in these organs. Sperm anomalies, temporary impotence, decreased libido, and hormonal imbalances have been reported in men exposed to 100–550 rad (1–5.5 Gy) (Birioukov et al. 1993). Similar effects in laboratory animals, such as decreased testes weights, decreased fertility, sterility, decreased sperm counts, chromosomal reciprocal transformations, sperm anomalies, and embryo mortality, have been reported at similar dose levels (Grahn and Carnes 1988; Pinon-Lataillade et al. 1991; Ramaiya et al. 1994; Searle et al. 1976; Shevchenko et al. 1992).

The data for reproductive effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

### 3.2.1.4 Teratogenic/Embryotoxic Effects

The rapidly dividing cells in the developing fetus, like those in the reproductive system, are also at a much higher risk of radiation damage, independent of the type of ionizing radiation, or the source or route of exposure, than slowly dividing, differentiated cells. The vast majority of the available literature reported numerous toxicological end points on the developing fetus associated with external radiation exposure. External exposure to the fetal animal by alpha and beta radiation is of no concern because α and β radiation cannot penetrate the mother's body tissues and the placental sac. Gamma radiation is very penetrating and can expose the fetus. The embryo/fetus is always uniformly exposed to external gamma rays from background radiation. There may also be partial body exposure from medical x rays or from internal exposure to a radionuclide such as $^{90}$Sr, which results in preferential uptake during fetal bone development. Of most concern in cases of human exposure are the effects of embryo organogenesis and how these changes will affect the individual as a child and an adult.

During the early days of development, the human embryo largely consists of a mass of undifferentiated cells, which are the cells most sensitive to the effects of ionizing radiation. These cells transform into more specialized (differentiated) cells at specific times during gestation and develop into the more organized tissues seen later at maturity. For the purposes of describing teratogenic and other effects of *in utero* exposure, gestation is divided into three major periods: preimplantation, 0-2 weeks, major organogenesis, 2–8 weeks, and the fetal period, 8–40 weeks (Brent et al. 1980). Central nervous system (CNS) injury of radiological importance results from exposure in the early fetal period. CNS development in humans can be subdivided into four basic periods of development after conception: weeks 1–7, weeks 8–15, weeks 16–25, and $25 weeks. During weeks 1–7, the cells that will later differentiate into neurons are steadily multiplying. During weeks 8–15, the population of neurons rapidly increases, and neurons migrate to their functional sites, and lose their ability to further divide. Between weeks 16 and 25, these neurons continue to develop, but more importantly, they undergo synaptogenesis in order to communicate. From week 25 on, the neurons continue to differentiate into more mature neurons, with continued growth of the cerebrum (cognitive thought and motor skills) and cerebellum (motor coordination) (BEIR V 1990; ICRP 1986).

**Fetal Central Nervous System Developmental Defects (Mental Retardation and Impaired Intelligence).** Analysis of human data from fetuses exposed to very high doses of radiation during the bombing of Hiroshima and Nagasaki suggests that the cells of the developing central nervous system are among the cells most sensitive to the effects of ionizing radiation in the developing human fetus. The major clinical effects on these susceptible cells were mental retardation and IQ reduction; these effects were observed after birth during childhood development. Human fetuses exposed to doses of ionizing radiation from 1 to 7 weeks after conception suffered no discernable ill effects after birth. A dose-dependent increase in mental retardation occurred in individuals who were irradiated *in utero* during weeks 8–15 after conception. Severe mental retardation in all 30 cases in the clinical sample was diagnosed before age 17, based on clinical impressions and not on IQ scores. A "no effect" threshold was seen for doses in the range of 20–40 rad (0.2–0.4 Gy); at a dose of 100 rad (1 Gy), the frequency of observed mental retardation was 43% (BEIR V 1988; ICRP 1986; Schull et al. 1988). Similar results were seen in fetuses exposed from weeks 16 to 25; however, the relative risk of mental retardation was significantly lower. No discernable adverse effects occurred in children exposed during the period from week 26 to birth. Although the mothers of the retarded children had suffered very large radiation doses, some groups have suggested that these CNS effects on their unborn children may not have been caused by radiation but by genetic variation, nutritional variation, bacterial and viral infections during pregnancy, and embryonic or fetal hypoxia (BEIR V 1990; ICRP 1986).

Intelligence quotient (IQ) test scores of children fetally exposed to high radiation doses during each of these time frames support the supposition that exposure to ionizing radiation during fetal development may cause adverse effects. The MRL is based on a combination of two studies, one by Schull et al. (1988) and one by Burt (1966). Schull et al. (1988) evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain. The end point measured was change in intelligence test scores. The effects on individuals exposed *in utero* during the atomic bombing of Hiroshima and Nagasaki were based on the original PE86 samples (n=1,759; data on available intelligence testing) and the clinical sample (n=1,598). The original PE86 sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy or more, and many more individuals in the dose range 0–0.49 Gy than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 m in Hiroshima and Nagasaki. Children exposed at greater distances or not present in the city were selected as controls. In 1955–1956, Tanaka-B (emphasis on word-sense, arithmetic abilities, and the like, which were associated with the more subtle processing of visual clues than their simple recognition and depended more on connectedness) and the

Koga (emphasis on perception of spatial relationships) intelligence tests were conducted in Nagasaki and the Koga test in Hiroshima. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurred 8–15 weeks after fertilization under both T65DR and DS86 dosimetric systems. These systems represent the best estimates of radiation doses to individual Japanese survivors using the best data available through 1965 and 1986, respectively. The T65DR dosimetry used site-specific data along with information obtained during later atomic bomb testing under arid conditions, whereas the DS86 dosimetry incorporated effects of high atmospheric humidity that existed when the weapons were exploded over Japan. The regression of intelligence score on estimated DS86 uterine absorbed dose is more linear than with T65DR fetal dose, and the diminution in intelligence score under the linear model is 21–29 points at 1 Gy. The regression of intelligence score on estimated fetal absorbed dose was linear for the exposed 8–15 weeks after fertilization and possibly linear for the 16–25 week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing exposure; the mean IQ scores decrease significantly and systematically with uterine or fetal tissue dose within the groups exposed at 8–15 and 16–25 weeks.

In summary, analysis of intelligence test scores at 10–11 years of age of individuals exposed prenatally showed that:

- There is no evidence of a radiation-related effect on intelligence scores among those individuals exposed within 0–7 weeks of fertilization or in the 26$^{th}$ week of gestation and beyond;
- The cumulative distribution of test scores suggests a progressive shift downwards in intelligence scores with increasing exposure to ionizing radiation (dose-response relationship);
- The most sensitive group was the 8–15 week exposure group. The regression in intelligence scores was found to be linear, with a 1-Gy dose resulting in a 21–29 point decrease in intelligence scores.

Using the Schull et al. (1988) data in conjunction with the observations of Burt (1966), an MRL of 0.004 Sv (400 mrem) was derived for acute-duration external radiation exposures.

**Embryo Organogenesis Defects and Body Weight Alterations.** Beta and gamma radiation have been demonstrated to induce embryo/organogenic defects in laboratory animals. As in the human fetus, the developing central nervous system of laboratory animals during specific stages of development is at varying degrees of risk from exposure to ionizing radiation. In laboratory animals, effects such as hydrocephaly, anencephaly, encephalocele, spina bifida, functional and behavioral effects, motor defects,

hyperactivity, and defects in learning, as well as a host of other defects have been reported (BEIR V 1990). For example, Bruni et al. (1994) studied the effects of low levels of ionizing radiation on embryogenesis. Pregnant Sprague-Dawley rats were exposed for 14–17 seconds on gestational days 9.5, 15, and 18 to 50 rad (0.5 Gy) of $^{60}$Co radiation. Irradiated rats and controls were sacrificed at prenatal intervals of 4 hours, 48 hours, and 10 days (term) after exposure. No statistically significant difference was seen in the number of embryos recovered per litter for control and irradiated embryos sacrificed 4 hours after exposure. With the exception of the neuroepithelium, no histopathological changes were observed in embryos in this group. In irradiated embryos, mitoses were reduced within the neuroepithelium; pyknosis and some necrosis of cells were apparent at this gestational interval. No significant difference was seen in the number of embryos recovered per litter, the crown-rump length, or the head length of irradiated embryos sacrificed 48 hours after irradiation compared to controls. Among the gross developmental abnormalities observed in embryos 48 hours after irradiation, excessive flexion of the embryo (seen in 3.7%) and abnormal flexion of the head (seen in 1.2%) were the only effects that appeared to possibly be radiation-induced. At term, no significant differences in litter size or resorption rates were observed in irradiated animals compared to the controls. Mean fetal body and placental weights were not significantly different. There was a higher incidence of developmental abnormalities in irradiated fetuses (9.7%) than in controls (4%), but this observation was not statistically significant. The most common anomalies were defects in ocular development; microphthalmia (small eyes) and anophthalmia (absence of eyes) were seen in 3% and 1.5% of irradiated fetuses, respectively. Scoliosis was also significant with a prevalence of 1%. Viscerally, abnormally positioned kidneys were found in 5.8% of irradiated fetuses and 7.1% of controls. Ureteric anomalies and hemorrhagic liver lesions were encountered in 2% and 11.5% of irradiated fetuses, respectively. No significant developmental differences were observed in the nervous system of irradiated versus control fetuses at term. The authors concluded that *in utero* doses of 50 rad (0.5 Gy) of gamma radiation during the period of early organogenesis can produce some irreversible defects that are discernable at term.

**External Malformations, Growth Retardation, and Death.** Many other types of birth defects in animals have been reported. Kusama and Hasegawa (1993) designed a study to precisely determine the radiosensitive period in the development of mouse embryos during which external malformations and growth retardation tended to occur. Pregnant mice were treated at various times during the gestation period with a single whole-body gamma radiation dose of 150 rad (1.5 Gy) delivered at a dose rate of 20 rad/minute (0.2 Gy/min) from a $^{137}$Cs source. Death of the embryo/fetus, especially during the early period of organogenesis, was most frequent in mice irradiated between days 6.75 and 8.25 of gestation.

There was no difference in radiosensitivity between male and female fetuses. Reduction of fetal body weight was found to be a good indicator of radiation effects. Body weights of all irradiated fetuses were significantly less than controls. The reduction in fetal body weights was marked in mice irradiated during the intermediate stage of organogenesis (between days 9.75 and 12.75 of gestation). The body weights of abnormal fetuses with external malformations other than exencephalia (exposed brain) and eventration were not significantly different from those of fetuses without external malformations. Exencephalia appeared most often in mice irradiated between 6.5 and 8.75 days of gestation (0.6–21.7%) and at a low frequency between days 10.25 and 10.75 of gestation (0.5–1.5%). Cleft palate appeared in mice irradiated between days 8.25 and 12.75 of gestation (1.1–20.5%). Micromelia, ectrodactyly, and polydactyly were observed in fore- and hindpaws. The forepaw malformations appeared in fetuses exposed on days 10.25–12 of gestation (0.8–46.2%). Hindpaw malformations showed two periods of high sensitivity, from days 7.5 to 8.75 (0.6–3.8%) and from days 10.25 to 12 (0.6–28.9%) of gestation. Shortened and/or bent tails were observed in groups irradiated from days 7 to 11.5 of gestation (0.7–32.5%), with the peak frequency among those irradiated on day 9.25 of gestation.

Other animal studies support the observation of increased incidences of birth defects after exposure to ionizing radiation. Devi et al. (1994) exposed the whole abdominal region of pregnant Swiss mice (n=25) to 5–50 rad (0.05–0.5 Gy) of $^{60}$Co gamma radiation (at a dose rate of 83 rad/min, 0.83 Gy/min) on postcoitus day 11.5. Increased fetal mortality and retarded growth was seen among the 50 rad (0.5 Gy) group. At this level, retarded growth was observed in 12% of fetuses, with body weight and body length decreased (7% and 3%, respectively). A significant reduction in head length, width, and brain weight was seen at 25 rad (0.25 Gy) and above. A significant increase in the incidence of microphthalmia was also observed at 25 rad (0.25 Gy) and above in 14% of fetuses. Zaman et al. (1992) also studied the effects of acute-duration prenatal radiation on myelination of the developing brain, as well as some physical parameters. Rats were treated with a single dose of gamma radiation (6.8, 15, or 150 rad, 0.068, 0.15, or 1.5 Gy) on the 20th day of pregnancy. At day 30, absolute brain, kidney, heart, and spleen weights of the 150 rad (1.5 Gy) treated group were significantly lower than that of any other treatment group. Relative brain, ovary, adrenal, kidney, liver, heart, spleen, and lung weights showed no significant differences among the lower treatment groups. At postnatal day 52, brain weight of the 150 rad (1.5 Gy) treated group was significantly lower than the other treatment groups and controls. No significant differences were seen in other organ weights at day 52. The relative weight of the cerebral cortex was significantly less than controls in the 150 and 15 rad (1.5 and 0.15 Gy) groups at day 30 and in the 150 rad (1.5 Gy) group on day 52 (9–11%). In addition, Reyners et al. (1992) evaluated the effects of radiation on fetal

brain development in pregnant Wistar rats exposed on gestation day (Gd) 15. Protracted gamma irradiation to total doses up to 80 rad (0.8 Gy) was performed with a $^{60}$Co source. The dose rate varied from 1 rad/day to 13.3 rad/day (0.01–0.133 Gy/day). Exposure was carried out either from Gd 12 to 16 (4 days) or from Gd 14 to 20 (6 days). $^{60}$Co gamma irradiation protracted over 4 days from Gd 12 to 16 significantly reduced the brain weight in 3-month-old rats by 3%, 4%, and 13% after 160, 350, and 560 rad (16, 35, and 56 Gy) exposures. Animals irradiated for 6 days from Gd 14 to 20 also showed a significant reduction in the 3-month-old brain weight of 5%, 4%, and 7% after exposures to 17, 34, and 80 rad (0.17, 0.34, and 0.8 Gy), respectively. The cingulum volume was also significantly decreased in the 80 rad group by 19%.

**Dental and Oral Cavity Development.** Ionizing radiation can also affect dental and oral cavity development. Lee et al. (1989) irradiated Beagle dogs *in utero* at 8, 28, or 55 days postcoitus or postnatally at 2, 70, or 365 days postpartum. Whole-body $^{60}$Co gamma radiation doses ranged from 0 to 380 rad (3.8 rad). After a threshold effect dose of 83 rad (0.83 Gy), there was an age-dependent dose-related increase in premolar hypodontia for dogs irradiated at 55 days postcoitus or 2 days postpartum. Dogs irradiated at 55 days postcoitus were the most sensitive, with fewer than 20% having normal teeth at doses above 83 rad (0.83 Gy). After irradiation at 28 days postcoitus, no effect was seen below doses of 120 rad (1.2 Gy). Similarly, Saad et al. (1991) exposed pregnant CD-1 Swiss albino mice on the 12th gestational day to an external gamma radiation dose of 400 rad (4 Gy). All irradiated fetuses presented clefts of the secondary palate but usually not cleft lip. The development of the maxillary and mandibular incisors was retarded in irradiated fetuses and was in early bell stage, whereas controls had elaborated their matrices.

**Fetal Blood Forming Organs.** Significant doses of ionizing radiation can also affect the fetal blood-forming organs. Koshimoto et al. (1994) mated female Wistar rats, and on the 13th, 14th, or 15th day of gestation, and then externally irradiated them with 50–800 rad (0.5–8 Gy) of $^{137}$Cs gamma radiation. Forty-eight hours later, the pregnant animals were sacrificed and the numbers of ovulations, implantations, and surviving fetuses were determined. Blood cell volume was measured, and fetal blood was collected. The numbers of erythrocytes and hepatocytes in the livers in the fetuses were counted. The number of blood cells in circulating blood after the fetuses were irradiated to 800 rad (8 Gy) on day 15 was significantly lower than the controls, and the formation of micronuclei was significantly increased at 50 rad (0.5 Gy) and above. The erythrocyte counts in the fetal liver were significantly lower than controls at 400 and 800 rad (4 and 8 Gy), and the ratio of the large hematocyte count to the small hematocyte count was significantly higher than controls at doses of 100 rad (1 Gy) and above.

**Reproductive Tract.** The *in utero* exposure to large doses of ionizing radiation can affect the forming reproductive tracts of male and female embryos. As an example, Inano et al. (1989) exposed pregnant rats to whole-body irradiation at Gd 20, with 260 rad (2.6 Gy) gamma rays from a $^{60}$Co source. It was found that the seminiferous tubules of the irradiated male offspring were remarkably atrophied with free germinal epithelium and contained only Sertoli cells. Female offspring also had atrophied ovaries. The testicular and ovarian weight in irradiated offspring were 18% and 34%, respectively, of controls. No oocytes or Graafian follicles were found in ovaries of the irradiated rats. Testicular tissue obtained from control and $^{60}$Co-irradiated rats was incubated with $^{14}$C-labeled pregnenolone, progesterone, 17-alpha-hydroxyprogesterone, and androstenedione as a substrate. Intermediates for androgen production and catabolic metabolites were isolated after the incubation. The amounts of these metabolites produced by the irradiated testes were low in comparison with the control. The activities of delta[5]-3-beta-hydroxysteroid dehydrogenase, 17-alpha-hydroxylase, C(17, 20)-lyase, and delta[4]-5-alpha-reductase in the irradiated testes were 30–40% of those in nonirradiated testes. The activities of 17-beta- and 20-alpha-hydroxysteroid dehydrogenases were 72% and 52% of controls, respectively. The activity of delta[5]-3-beta-hydroxysteroid dehydrogenase of the irradiated ovary was only 19% of the control. The authors note that these results suggest that high-dose $^{60}$Co irradiation of the fetus *in utero* markedly affects the production of steroid hormones in the testes, ovaries, and adrenal glands after birth.

**Behavioral Alterations.** Behavioral changes have also been noted in laboratory animals after birth when exposed to certain doses of ionizing radiation during the embryo stages of development. Minamisawa et al. (1992) investigated social behavior, in particular aggressive behavior (AB), in mice exposed prenatally to ionizing radiation. Pregnant C57BL/6 mice (n=3) were exposed to whole-body gamma radiation from a $^{137}$Cs source on Gd 14. The dose rate to the midline of the mouse was 25 rad per minute (0.25 Gy/min) and doses of 0, 100, and 200 rad (0, 1, and 2 Gy) were given. AB in first-generation (F1) hybrid male offspring was studied. The number of instances of AB was significantly higher in the 100-rad (1 Gy) group than in controls during the first 45 minutes of observation. The AB of the 200-rad (2 Gy) group was significantly more intensive than that of the control group. There is little information in the literature with which to compare these findings.

In a similar study, Zaman et al. (1993) treated adult female Fischer 344 rats with a single dose of total-body gamma radiation (6.8, 15, or 150 rad [0.0068, 0.15, or 1.5 Gy]) on the 20th day of gestation (thus, the offspring received the radiation doses on the 20th day of prenatal life). During the 3 weeks of the offspring's postnatal life, changes in pivoting, crawling, negative geotaxis, cliff avoidance, hindlimb

support, eye opening, and tooth eruption were studied. Pups irradiated with 150 rad (1.5 Gy) exhibited significantly lower pivoting than any other group on days 15–16 of the observation period. No significant differences were observed between treatment groups for crawling, geotaxis, or hindlimb support when suspended. Cliff avoidance was recorded from days 3 to 10 postnatally. Cliff avoidance was significantly different in the 15 and 150 rad (0.15 and 1.5 Gy) groups compared to the 6.8 rad (0.068 Gy) group and controls on day 8 only; however, the mean score was not significantly different in the 15 rad (0.15 Gy) group. Data from this study suggest that radiation affects several of the tested locomotion parameters. Based on the data presented in this study, it appears that areas of cerebral cortex including the somatosensory and sensory cortex, the primary cortex, and the premotor cortex were adversely affected by doses of 150 rad (1.5 Gy) when delivered around gestation day 20.

**Sensorimotor Effects.** Norton and Kimler (1987) also investigated the early postnatal behaviors involving sensorimotor integration and the thickness of the sensorimotor cortex in prenatally irradiated rats which received a dose of 100 rad (1 Gy) from a $^{137}$Cs source. Performance in the negative geotaxis test was poorer in irradiated rats than in controls. Rats irradiated on Gd 17 were unable to equal the performance of either controls or rats irradiated on Gd 11 in the reflex suspension test. No gait alterations were seen in the irradiated rats. In a later study, Norton and Kimler (1990) exposed pregnant Sprague-Dawley rats to whole-body gamma radiation from a $^{137}$Cs source on Gd 15 to doses of 25, 50, 75, or 100 rad (0.25, 0.5, 0.75, 1.0 Gy). The fetuses of irradiated dams were examined 24 hours after irradiation for changes in the cells of the cerebral mantle of the developing brain. Changes were seen in those rats treated with 50 or more rad ($0.5 Gy). Cortical thickness of the cerebral mantle was not significantly altered. The number of pyknotic cells, the number of macrophages, the nuclear area, and the number of mitotic cells were altered in a dose-related way. The number of mitotic figures in the ventricular zone was significantly reduced and the number of macrophages was significantly increased in fetuses from the 50-, 75- and 100 rad (0.5, 0.75, and 1 Gy) treatment groups. The nuclear area in fetuses prenatally exposed to 100 rad (1 Gy) was significantly increased. In fetuses prenatally exposed to 50 rad (0.5 Gy), the nuclear area of subventricular zone cells was significantly increased compared to controls 12 hours postirradiation but returned to almost the control value at 24 hours postirradiation. The number of macrophages in the ventricle and in the cortical mantle was significantly increased at 12 and 24 hours in fetuses prenatally exposed to 50 rad (0.5 Gy). Several vesicles containing nuclear fragments were present in each macrophage at these times. The number of mitotic figures in the ventricular zones was significantly increased at 3 and 6 hours postexposure and significantly decreased at 12 and 24 hours postexposure in fetuses prenatally exposed to 50 rad (0.5 Gy) compared to controls. Pyknotic cells

developed rapidly after irradiation with 50 rad (0.5 Gy). At 3 hours postirradiation, the total number of pyknotic cells in the cortical mantle had increased from nearly 0 to 166. This number increased slightly from 3 to 6 hours and then declined from 12 to 24 hours. The number of pyknotic cells in the ventricular and subventricular zones decreased while the proportion in the intermediate and cortical plate zones increased. Both the percentage and number of pyknotic cells increased with time in the two latter zones. A positive correlation between the number of pyknotic cells and the number of macrophages developed with time. At 3 hours after irradiation, about 60% of pyknotic cells were found in the subventricular zone and about 25% in the intermediate zone and cortical plate. The number of such cells in the upper layers of the cortex steadily increased up to 24 hours, at which time about 70% of pyknotic cells were in these two layers.

In summary, the developing fetus, with its rapidly dividing cell characteristics, has been an area of intense study relating to the effects of radiation, particularly for large gamma radiation doses. Laboratory animal models have been used to delineate many of these effects. Radiation, above a threshold dose of about 25 rad (0.25 Gy) can impair development of embryonic structures, in particular the structures of the central nervous system when delivered during a sensitive period. Radiation affects specific cells of the developing nervous system at specific times during its developmental process, although the exact mechanisms behind these alterations are not known. Many of these reports include descriptions of decreased fetal body weights (Devi et al. 1994; Minamisawa et al. 1990; Norton and Kimler 1987; Zaman et al. 1992) and developmental anomalies, such as necrosis of neuroepithelial cells, microphthalmia, anophthalmia, scoliosis, decreased myelination of the brain, hypodontia, cleft palate, micromelia, ectrodactyly, polydactyly, as well as many more defects (Bruni et al. 1994; Kusama and Hasegawa 1993; Lee et al. 1989; Reyners et al. 1992; Saad et al. 1991; Zaman et al. 1992) at doses of <300 rad (3 Gy). Social behavior changes have also been reported in male mice at doses of 100 rad (1 Gy) and higher (Minamisawa et al. 1992). Locomotor difficulties have also been reported (Norton and Kimler 1987, 1988; Zaman et al. 1993) as well as reproductive organ anomalies (Inano et al. 1989). From these animal studies, it is clear that the developing embryo and fetus are subject to damage from radiation at doses greater than 25–50 rad (0.25– 0.5 Gy).

Data for developmental effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

### 3.2.1.5 Central Nervous System (CNS) Effects

As a whole, the central nervous system of the adult human and laboratory animal is extremely resistant to the effects of radiation (see Table 3-2). In contrast to the rapidly dividing cells of the gastrointestinal and hematopoietic systems, the central nervous system has a relatively static population of cells, with cell mitosis occurring between long intervals of latency, if at all. This allows cells to be exposed to much larger doses of radiation because the cells have much more time to repair themselves before they multiply. The brain appears to be sensitive to ionizing radiation only at extremely large doses; a dose of approximately 1,500 rad (1.5 Gy) was necessary to produce discernable deterministic effects. Necrosis of the brain (associated with demyelination and cerebral vascular damage) may occur within 3 years after a 5,500 rad (55 Gy) dose received over a 6-week time frame. Demyelination and necrosis of neurons in the white matter of the spinal cord can also develop within 6 months after exposure to high doses (>6,000 rad or 60 Gy) of radiation. These are very large doses of radiation.

Birioukov et al. (1993) reported that one man exposed to 200–350 rad (2–3.5 Gy) had clinical symptoms such as permanent headache and vision impairment after accidental exposure to gamma radiation during and after the Chernobyl atomic power plant accident. Reports are available that describe the effects that radiation has on the nervous system of the developing embryo in laboratory animals (Minamisawa et al. 1992; Norton and Kimler 1987, 1990). Harmful effects have been found from extremely high doses of radiation to adult animals. Cockerham et al. (1986) explored the effects of radiation on early transient incapacitation (ETI) and performance decrement (PD) in support of nuclear warfare research efforts. Rhesus monkeys (n=6) were exposed to a lethal whole-body total dose of 10,000 rad (1,000 Gy) from a $^{60}$Co source. Autopsy findings included destroyed nerve cells (neurons), supporting tissue in the brain (glial cells), and lining cells (endothelium) of the capillaries in the brain.

Bassant and Court (1978) exposed rabbits to a $^{60}$Co gamma ray source, with a mean absorbed dose of 450 rad (4.5 Gy). According to the authors, the $LD_{50/30}$ for rabbits ranges from 600 to 650 rad (6–6.5 Gy). Following irradiation, the hippocampal cellular activity was highly disturbed, as described by the EEG activity.

Data for neurological effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

### 3.2.1.6 Respiratory and Cardiovascular Effects

The respiratory tract has long been known to be a target organ of both internal and external radiation. Respiratory effects have been reported in humans (Stavem et al. 1985) who had received radiotherapy for breast cancer and those who had been accidentally overexposed, as well as in laboratory animals (Rezvani et al. 1989; Salovsky and Shopova 1992). No harmful effects have been seen in the millions of people who receive occasional diagnostic x rays of the chest. Local injury is tolerated much more than diffuse injuries. Irradiation of large portions of one or both lungs initially results in alterations in blood flow, initially manifested as edema, and later as pneumonitis and pulmonary fibrosis, depending on the total dose received. Radiation pneumonitis, followed by pulmonary fibrosis (i.e., fibrosis of alveolar structures involving changes in the ratios of some pulmonary collagens), are two of the most commonly reported aberrations in laboratory animals following an inhalation of large activities of radioactive material (Benjamin et al. 1978, 1979; Brooks et al. 1992; Hahn et al. 1975, 1981; Lundgren et al. 1980a, 1991).

The mechanism behind the induction of radiation pneumonitis is not completely understood; however, a vascular component (comprised of sloughing and of dead and dying endothelial cells that may lead to capillary leakage) has been suggested. Damage to type II pneumocytes, which can lead to serious alterations in the amount of surfactant phospholipids and to lung inflammation, has also been considered. The role of type I pneumocytes, which by necrosing and sloughing leave denuded basement membranes and alveolar debris, may also be significant. Any one or all of these mechanisms may be involved in the development of pneumonitis. Fibrosis, a serious sequela of pulmonary inflammation due to large populations of cells dying and not being replaced, is seen in the lungs after exposure to ionizing radiation at moderate to high doses or to fibrogenic dusts, such as quartz and asbestos or even aluminum (ATSDR 1999a). A more in-depth discussion of radiation pneumonitis and subsequent fibrosis after exposure to ionizing radiation is available in a report by Coggle et al. (1986).

Most respiratory studies have focused on the effects of ionizing radiation on the lungs when associated with inhaled insoluble (and, to a lesser degree, soluble) particles. Most of these studies looked at acute inhalations of large quantities of radioactive material resulting in high initial lung burdens and cumulative radiation doses on the order of hundreds of rad (several Gy). After the radioactive material was inhaled, clinical signs were related to the organ system which received the major radiation dose during and after redistribution of these particles had occurred. Important aspects of this redistribution related to whether these radionuclides were in a soluble or insoluble form and to the size of the inhaled particle. Soluble

particles tended to dissolve in the lung matrix and redistribute based on chemical mechanisms; then they had the potential to affect other organ systems. These soluble particles tended to deliver a higher dose rate to the lungs shortly after inhalation; the rate tended to decrease rapidly as the material was dissolved and the radionuclide redistributed to other organs via the normal lung clearance mechanisms. Soluble particles deposited in the respiratory tract tended to result in lower overall lung dose and higher overall distal organ dose over time when compared to insoluble particles because they exposed the lung tissue for a shorter period of time.

Unlike the soluble particles, the bulk of the inhaled insoluble particles tended to remain for long periods of time in the lungs (several days to several years), irradiating the tissues and depositing large radiation doses to the tissue immediately around the particles. Some fraction of these particles would initially be coughed up or removed by the ciliary clearance mechanism and then swallowed during the first few days after exposure, thereby exposing the gastrointestinal tract as the particles passed through and cleared the body. In addition, smaller particles (1–3 μm) tended to penetrate to the deeper regions of the lungs (terminal bronchioles and alveoli); larger (>6 μm) particles were deposited in the upper respiratory tract (trachea, conducting airways). The effect of inhaled radioactive particles, therefore, varied with the size distribution and solubility of the inhaled particles, as well as the type and quantity of the inhaled radioactivity.

Respiratory insufficiency was a common finding in many studies following high radiation doses to the lungs. This was manifested clinically as increased respiratory rates, increased abnormal lung sounds and cyanosis, decreased lung volumes, and total lung capacity, and compliance (common but not pathoneumonic symptoms of pneumonia). These clinical symptoms were most likely related to inflammatory and fibrotic changes occurring within the lungs. This observation is supported by radiographic, gross, and histopathological evidence, such as increased radiographic focal or diffuse lung-field densities, and by interstitial, perivascular, peribronchial, and pleural fibrosis; emphysema; inflammation; vascular damage; fibrin exudation; congestion; and hemorrhage (Benjamin et al. 1976; Hahn et al. 1976; Lundgren et al. 1991).

Numerous assessments of human exposure to inhaled radionuclides (with no dermal or oral component) have been identified in the open literature. A group of 26 workers inhaled quantities of $^{239}$Pu dust that were many times larger than acceptable occupational standards. These workers have been followed medically since the inhalation in 1944. To date, one person has died from heart disease and one from bone cancer. Another report involved a U.S. military airplane crash near Palomares, Spain, in January

1966. The aircraft was carrying four thermonuclear weapons containing $^{239}$Pu. Two of the devices were recovered, and the other two devices detonated their conventional explosives and released fissile material upon ground impact. Partial ignition (chemical burning) of the fissile material resulted in a cloud formation that contaminated approximately 2.25 km$^2$ of farmland. The deposition density of alpha emitters was 32.4 μCi/m$^2$ (1.2 MBq/m$^2$); estimates of the inhaled and ingested dose from $^{239}$Pu and $^{240}$Pu were derived. Of the 714 people examined through 1988, 124 had urine concentrations of Pu greater than the minimum detection limits. An estimate from Iranzo et al. (1987) states that the 70-year committed effective dose for 55 of those 124 people, due to inhalation of radioactive particles, was 2–20 rem (0.02–0.2 Sv); however, no acute respiratory effects were reported and there has apparently been no long-term follow-up of these individuals.

There is a considerable database available on the effects seen from inhaled radionuclides in laboratory animals. For example, Hobbs et al. (1972) exposed Beagle dogs to initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, and 110 μCi (133, 67, 44, 29, 15.8, and 4 MBq) $^{90}$Y/kg body weight. The AMADs of the aerosols used ranged from 0.8 to 1.2 μm. Death was reported in 21 of 33 dogs exposed within 7.5 and 163 days postexposure, with their initial lung burdens ranging from 670 to 5,200 μCi/kg causing cumulative radiation doses through time of death of 8,400 to 55,000 rad (84–550 Gy). Clinical signs in the dogs that died included progressive increase of respiratory rates, abnormal lung sounds on auscultation, anorexia, progressive weight loss, and eventual cyanosis of the mucous membrane. Additionally, thoracic radiographs showed marked, generally diffuse nodular increases in density of lung fields. The authors note that clinical signs did not differ from high to low doses; however, the time to the onset and the duration of the illness varied considerably. A dose response could be demonstrated with these exposures: “acute symptoms” occurring 7–10 days after inhalation, with initial lung burdens of 1,700–5,200 μCi/kg (62–190 MBq/kg) and doses to the lungs of 21,000–55,000 rad (210–550 Gy); “subacute symptoms” with signs of respiratory insufficiency 3–4 weeks postexposure, initial lung burdens of 1,000–2,400 μCi/kg (37–89 MBq/kg) and doses to the lungs of 13,000–29,000 rad (130–290 Gy); “subacute to chronic symptoms” appearing at 6–8 weeks, which included a gradual deterioration in the animals' condition. Animals in this group had initial lung burdens of 670–760 μCi/kg (25–28 MBq/kg) and cumulative radiation doses to the lungs of 8,400–9,400 rad (84–94 Gy). Pathological findings at necropsy included pulmonary and pleural fibrosis, occlusive pulmonary vascular lesions, metaplasia and/or hyperplasia of terminal bronchiole and alveolar epithelium, right heart dilation, and hypertrophy. Small indurated hemorrhagic areas near the ventricular junction were present in the right atria of the hearts of 7 of the 12 dogs that died 64–92 days postexposure. Infarctions of the right atria were found in some animals.

Similarly, Muggenburg et al. (1988) exposed 216 Beagle dogs by inhalation to initial lung burdens of 3–54 μCi (0.1–2 MBq) $^{239}$Pu/kg monodisperse $^{239}PuO_2$ aerosols with AMADs of 0.75, 1.5, or 3.0 μm, which produced a protracted alpha irradiation dose to the lungs. From the group of 78 dogs which survived to 7.1 years post-inhalation, 20 were selected for cardiorespiratory function tests and further clinical evaluation. Of these 20 dogs, 10 were selected because they had persistent respiratory frequencies of 40 breaths/min for more than 1 year (group I). The second 10 dogs were selected because they had similar or slightly lower plutonium lung burdens at the time of inhalation as the dogs in group I, but had normal respiratory frequencies (group II). Ten controls were used (group III). The average dose to the lungs through 2,600 days after inhalation for the dogs in group I ranged from 230 to 3,200 rad (2.3 to 32 Gy) and for the dogs in group II, from 80 to 1,570 rad (0.8 to 15.7 Gy). Respiratory tract injury was again first observed as an increased respiratory frequency on average 3.4 years after inhalation; this change in breathing pattern persisted for at least 1 year. Only the dogs in group I with signs of lung injury had a mild respiratory function disorder consisting of smaller lung volumes, decreased total lung capacity, vital capacity, functional residual capacity, reduced dynamic and quasistatic compliance, and increased respiratory frequency and minute volume. Carbon monoxide diffusing capacity was significantly reduced in both groups I and II. These findings indicate that alpha irradiation of the lungs of humans could produce restrictive lung disease at long times after initial inhalation.

In addition to alterations in respiratory rates and respiratory function, pneumonitis and pulmonary fibrosis are two of the most commonly reported respiratory effects in animals (and humans) after lung exposure to large activities of inhaled radionuclides (Coggle et al. 1986). Hahn et al. (1975) studied the radiation dose of $^{90}$Y to the upper respiratory tract in Beagles exposed by nose-only inhalation to aerosols of $^{90}$Y in fused clay. Initial whole-body burdens ranged from 23 to 65 mCi (850–2,400 MBq), with initial lung burdens ranging from 9 to 35 mCi (520–1,300 MBq). A rapid initial decrease in body burden, typical of an insoluble material deposited by inhalation, was due to the clearance of particles from the upper respiratory tract entering the gastrointestinal tract. Of the 7 dogs surviving 27–29 days, 6 dogs exposed to 14–35 mCi initial lung burden developed radiation pneumonitis. Radiation pneumonitis was characterized by accumulations of alveolar macrophages, bizarre alveolar lining cells, and alveolar hemorrhage; vasculitis was the most consistent histopathologic finding. Benjamin et al. (1976) exposed 6 Beagle dogs to a nose-only inhalation of $^{90}$Y, $^{144}$Ce, or $^{90}$Sr in fused aluminosilicate particles (FAP). The initial lung burdens were 560, 46, and 28 μCi/kg (21, 1.7, and 1 MBq/kg) for $^{90}$Y, $^{144}$Ce, and $^{90}$Sr, respectively. Deterioration in the health of the dogs exposed to $^{90}$Sr included an increased respiratory rate, dyspnea, cyanosis, and dry and moist rales. Increased radiographic focal or diffuse lung-field

densities, with clear evidence of ventricular enlargement, was apparent. The lungs of dogs exposed to $^{90}Y$ and $^{144}Ce$ showed radiation pneumonitis characterized by interstitial, perivascular, peribronchial, and pleural fibrosis, focal emphysema, and acute and chronic inflammation with increased numbers of alveolar macrophages. Vascular damage included congestion, hemorrhage, fibrin exudation, and occasional vessels with fibrinoid necrosis or proliferation. Epithelial changes included denudation of terminal bronchioles and alveolar ducts, with regeneration of bizarre lining cells and proliferation of bizarre, hypertrophied alveolar lining cells. Adenomatous epithelial proliferation and squamous metaplasia were common findings in the $^{90}Y$ dogs.

Later, Benjamin et al. (1978) again exposed Beagles to $^{144}Ce$ in FAP by nose-only inhalation using particle sizes 1.4–2.7 μm. Initial lung burden ranges were around 25–35 μCi/kg body weight in dogs sacrificed or those that died between 1.4 and 4.1 years postexposure. The cumulative absorbed lung doses to death for these groups of dogs ranged from 27,000 to 47,000 rad (270–470 Gy). Dogs were sacrificed at half- to full-year intervals from 1.5 to 4 years. By 2 years after exposure, more than 90% of the radiation dose had been delivered. Beyond that time, radiation pneumonitis and pulmonary fibrosis were evident in approximately 80% of the dogs. Other reports of radiation pneumonitis and/or pulmonary fibrosis have been described in dogs (Benjamin et al. 1979; Hahn et al. 1976), monkeys (Brooks et al. 1992; Hahn et al. 1987; LaBauve et al. 1980), mice (Lundgren et al. 1980a, 1981, 1991), and hamsters (Lundgren et al. 1983).

Some laboratory animal studies were found that dealt with the effects of external radiation on the respiratory tract. In one study, Rezvani et al. (1989) determined the effects of external radiation on the diaphragmatic lobe of the left lung in female large white pigs irradiated with single doses of 900–1,470 rad (9–14.7 Gy) of $^{60}Co$ gamma rays at a dose rate of 80 rad/min (0.8 Gy/min). Standard lung function tests were performed prior to irradiation and at 4 and 13 weeks after irradiation, then at 13 week intervals up to 104 weeks. At 104 weeks after irradiation, the animals were sacrificed and the lungs were excised and examined for gross changes. A marked impairment in the ventilation capacity of the lungs 4 weeks after irradiation was seen, but was not considered to be dose-dependent. After a dose of 900 rad (9 Gy), the initial impairment in lung function was resolved within 13 weeks, while at 1,470 rad (14.7 Gy) damage persisted. There was an elevation in the breathing rate at 4 weeks after irradiation, which was most marked in animals irradiated with the highest doses; however, the breathing rate returned to normal within 13 weeks at all dose levels. At 104 weeks after irradiation, postmortem examination revealed only one case of adhesion between the lung and chest wall. In animals irradiated with $1,090 rad (10.9 Gy), atrophy of the irradiated left lobe of the left lung was seen. This was particularly

characteristic in all lungs irradiated with 1,470 rad (14.7 Gy) in which the lungs showed severe atrophy. At 1,280 rad (12.8 Gy), a general and severe thickening of the interlobular septa was seen in some animals. The authors calculated a 50% effective dose ($ED_{50}$) value for pathological changes (fibrosis and focal scarring) in the lungs of 1,112 rad (11 Gy).

With regard to external exposure to radiation, Salovsky and Shopova (1992) exposed male Wistar rats to 0, 400, 800, or 1,500 rad in a single whole-body dose in order to study the changes present in broncheo-alveolar tissue after exposure to ionizing radiation. Eight animals of each group were sacrificed on days 1, 5, and 15. Prior to sacrifice, a broncheoalveolar lavage was performed. The lavage fluid was analyzed for lactase dehydrogenase (LDH), alkaline phosphatase (APH), acid phosphatase (AcPH), angiotensin converting enzyme (ACE), and protein content. LDH activity was decreased on day 1 in the 1,500 rad (15 Gy) group. At day 5, the 400 and 800 rad (4 and 8 Gy) groups LDH levels were significantly decreased by 30% and 49%, respectively. No significant difference was observed at day 15. Both APH (31–41%) and AcPH (40–67%) were significantly decreased on day 1 in all irradiated groups. In the 800 rad (8 Gy) group, APH was significantly increased on day 15 (203%). ACE activity was examined only on day 1, with a significant increase in ACE in the 800 rad (8 Gy) (190%) and 1,500 rad (15 Gy) (187%) groups. Protein content decreased significantly only in the 1,500 rad (15 Gy) group, measured only on day 1. ACE is normally bound to lung endothelial cell surfaces, with increased concentrations suggesting endothelial cell injury. Increased protein content in the broncheoalveolar lavage fluid (BALF) indicates vascular permeability changes due to adverse events in the endothelial cells lining the capillaries. LDH, APH, and AcPH are normally intracellular enzymes, and their release into the extracellular domain indicates lung cellular membrane damage. From these data, it appears that LDH decrease may provide a non-specific biomarker of exposure to ionizing radiation at 1 week after exposure has occurred, whereas APH increase would be a non-specific biomarker of exposure at 2 weeks after exposure, to higher doses of ionizing radiation.

No harmful radiation effects on the heart have been seen at dose levels below hundreds of rad (tens of Gy). However, cardiovascular effects have been reported after exposure to inhaled radioactive material that led to very high radiation doses to the heart. The study described earlier by Muggenburg et al. (1988) noted no abnormal cardiac function parameters in any of the dogs studied; however, Hobbs et al. (1972) reported cardiac lesions in 33 Beagle dogs exposed in groups to mean initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, and 110, μCi (133, 67, 44, 29, 15, 8, and 4 MBq) of $^{90}Y$/kg body weight. Electrocardiogram changes, consistent with the right heart enlargement and/or conduction defect, were

observed in 5 of the animals that died 64–92 days postexposure after receiving a dose of 8,400 rad (84 Gy). Pathological cardiac findings included right heart dilation and hypertrophy. Small indurated hemorrhagic areas near the ventricular junction were present in the right atria of the hearts of 7 of the 12 dogs that died 64–92 days postexposure. Infarcts of the right atria were also found in some animals. ECG changes occurred in 5 of 12 and hemorrhagic areas were found near the ventricular junction in the right atria of 7 of 12 dogs that died 64–92 days after exposure.

Durakovic (1986a) studied cardiac function in male Beagle dogs that received 3,000, 6,000, or 10,000 rad (30, 60, or 100 Gy) of gamma radiation applied bilaterally to the precordium. The electrocardiograms remained normal after irradiation at all dose levels. The atrium, right and left ventricle, and papillary muscle of every dog all showed focal areas of perivasculitis. No evidence of focal necrosis was observed. The left ventricular ejection fraction (LVEF) did not show statistically significant decreases until 58–70 days after the irradiation, when a marked impairment of heart function was finally observed.

With regard to cardiovascular effects and external exposure to ionizing radiation, Stavem et al. (1985) reported a case of a 64-year-old male worker who accidentally received a large dose of gamma radiation in a facility that used ionizing radiation for sterilization. He was exposed for only a few minutes. From spectroscopic analyses of electron-spin resonance in irradiated material, the following mean doses were estimated: whole body, 2,250 rad (22.5 Gy); bone marrow, 2,100 rad (21 Gy); and brain, 1,400 rad (14 Gy). The dose to nitroglycerin tablets that were in the worker's pocket at the time was 4,000 rad (40 Gy). The worker developed an ARS and an autopsy was performed after death. The left ventricle of the heart was hypertrophic and the anterior descending ramus of the coronary artery was markedly stenotic; however, it was not clear whether this was an age-related effect or directly related to the effects of the radiation since much larger doses to animals are needed to produce such effects.

In summary, respiratory effects have been reported in humans (Stavem et al. 1985) as well as in laboratory animals (Rezvani et al. 1989; Salovsky and Shopova 1992) exposed to very high doses from internal and external sources of radiation because the respiratory system appears to be resistant to high doses of radiation. Most research has focused on radiation effects on the lungs when associated with inhaled insoluble (and, to a lesser degree, soluble) particles. These studies were acute, high-dose exposures resulting in high initial lung burdens on the order of several millicuries (tens of thousands of Bq), which resulted in cumulative doses in the thousands of rad (tens of Gy). After the radioactive material was inhaled, clinical signs were related to the organ system that received the major radiation

dose. Soluble particles dissolved in the lung and redistributed, depending on the radionuclide, to the liver or bone to induce toxic effects in those organ systems. After an initial clearance phase from the lungs, from which a portion of the initial lung burden was transferred to the gastrointestinal tract, the balance of the insoluble particles remained for long periods of time in the lung (days to years), irradiating the tissues closest to their immediate lung location and leaving the lungs very slowly. The effect of ionizing radiation on the lungs varied with the dose and length of exposure of the lung tissue. Respiratory insufficiency, manifested clinically as increased respiratory rates, increased abnormal lung sounds, and cyanosis, was a common finding in these studies (Hobbs et al. 1972; Muggenburg et al. 1988), in association with decreased lung volumes, total lung capacity, and compliance (common but not pathognomonic of pneumonia) (Muggenburg et al. 1988). These clinical signs are most likely related to inflammatory and fibrotic changes occurring within the lungs. This observation is supported by radiographic, gross, and histopathological evidence, such as increased focal or diffuse radiographic lung-field densities, and by interstitial, perivascular, peribronchial, and pleural fibrosis; emphysema; inflammation; vascular damage; fibrin exudation; congestion; and hemorrhage (Benjamin et al. 1976; Hahn et al. 1976; Lundgren et al. 1991). Radiation pneumonitis, followed by pulmonary fibrosis (fibrosis of alveolar structures involving changes in the ratios of some pulmonary collagens), are two of the most commonly reported aberrations in laboratory animals following the inhalation of radioactive substances (Benjamin et al. 1978, 1979; Brooks et al. 1992; Hahn et al. 1975, 1981; Lundgren et al. 1980a, 1991). Radiation pneumonitis is characterized by sloughing of dead and dying endothelial cells that may lead to capillary leakage. Damage to type II pneumocytes, which can lead to serious alterations in the amount of surfactant phospholipids and lung inflammation, has also been considered. The role of type I pneumocytes, that by necrosing and sloughing leave denuded basement membranes and alveolar debris, may also be significant. Alterations in cardiovascular functions could not be definitively linked to ionizing radiation after inhalation or external ionizing radiation exposures in laboratory animals (Durakovic 1986a; Hobbs et al. 1972; Muggenburg et al. 1988) or in one man exposed to external ionizing radiation (Stavem et al. 1985); however, some changes in regional cerebral blood flow were noted in one study (Cockerham et al. 1986) that used Rhesus monkeys as a model and these were probably linked to histamine release. However, all of these effects are due to very high radiation doses, which are extremely unlikely at radioactive waste sites.

Data for respiratory and cardiovascular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

### 3.2.1.7 Ocular Effects

The lens of the eye is not among the most radiosensitive tissues in the body, but it has less efficient repair capabilities than many other tissues. This allows radiation damage to build up with less repair, even when doses are fractionated or delivered at low dose rates. Exposure of the lens to sufficient doses of ionizing radiation results in cataract formation, which can range from minimally detectable opacities that do not impair vision to blindness. The target cells in the lens are the epithelial cells on the interior surface of the anterior capsule of the lens. These cells differentiate into lens fibers, which are normally transparent. The function of the lens is to focus the light entering the pupil onto the retina. After exposure to ionizing radiation, these cells fail to divide to produce lens fibers of the appropriate length or transparency. These defective fibers then tend to migrate to the posterior pole of the lens, where they can be seen ophthalmologically as a small, opaque dot. The appearance of the opacities can appear anytime between 0.5 and 35 years postexposure. Occurrence is affected by the dose, dose rate, and the type and energy of the radiation. Cataracts can be induced with as little as 2 Gy (200 Gy) of x ray irradiation (Adams and Wilson 1993). Data from those victims exposed to large doses of ionizing radiation after the bombings of Hiroshima and Nagasaki show a threshold of 0.6–1.5 Gy (60-150 rad) of low LET radiation. However, typical human exposures over a long period of time are thought to have a vision impairing threshold greater than 8 Gy (800 rad) (BEIR V 1990).

The effects of ionizing radiation on the eye have been reported in some human exposure cases. Ham (1953) described the radiogenic cataracts in cyclotron physicists from mixed gamma-neutron doses of 700–1,000 rad (70–100 Gy) to the lens. Klener et al. (1986) reported on a human case study in which a male technician was accidentally irradiated by a sealed $^{60}$Co source he had been installing. His health status was followed for 11 years after the accident. A film dosimeter worn during the accident indicated it received an exposure of 159 rad (1.59 Gy), but the dose to his eye was not reported. Changes in the lens of the left eye began to appear gradually, leading to the deterioration of visual acuity. Later, opacities of the lens of the right eye were also found.

Schweitzer et al. (1987) exposed Beagle dogs to single, bilateral, whole-body exposures to $^{60}$Co gamma radiation at various stages during fetal ocular development. Dogs were irradiated during middle or late pregnancy at 28 or 55 days postcoitus (dpc) or as neonates on the second postpartum day (ppd), with mean whole-body doses ranging from 100 to 386 rad (1–3.86 Gy). The dose to the eyes was essentially equivalent to the whole-body dose. For dogs exposed on ppd 2, the most prominent fundic alteration on

or before 70 days of age was a reduction in arterioles and a narrowing of the venules. The venules were dull, the tapetal fundus mottled in appearance, the nontapetal fundus lighter in color than controls, the optic disc paler, and the eyes characterized by a generalized slight haziness of the ocular media. Dogs sacrificed at 2–4 years of age had more marked reductions in arterioles and attenuation of the venules. Hyperreflectivity from the eye was found, and homogeneity was often lost in affected eyes. General and focal degenerative lesions were evident as were color changes. Partial tapetal atrophy with increased pigmentation in the area previously occupied by tapetum was noted in some eyes. Loss of color and hyperreflectivity were related to focal loss of pigment and thinning of atrophic retinal foci. With severe retinal atrophy or degeneration, choroidal circulation was seen in the nontapetal fundus. Retinal lesions were progressive in severity and extent, and the degree of injury was similar for both eyes. A correlation was seen between lesions (mostly in the retina and lens) and radiation treatment, with respect to both age at exposure and radiation dose. Due to fixation and sectioning artifacts, most lenses couldn't be adequately evaluated histopathologically. Retinal dysplasias and atrophy were the most striking lesions seen. The stage of development at exposure had a marked effect on the distribution of retinal lesions. The most severe changes were seen in the portion of the retina undergoing differentiation at the time of the insult. In dogs sacrificed at 70 days of age, the lesions were primarily dysplasias, consisting of ectopic nuclear aggregates in the photoreceptor layer, retinal folds, and retinal rosettes. With increasing age, there appeared to be progression of the extent of the clinically evident lesions, and there was a change in the nature of the lesions from dysplasia to atrophy. This was accompanied by marked attenuation of the retinal vasculature. In dogs exposed on ppd 2, retinal degeneration was evident in all dogs sacrificed at 70 days, 2 years, or 4 years of age. Retinal dysplasias were evident in all dogs sacrificed at 70 days of age and in 4 of the 13 dogs sacrificed at 2 years. Retinal dysplasia was not evident in dogs sacrificed at 4 years. Atrophy in dogs exposed on ppd 2 was evident in 19 of the 20 dogs sacrificed at 70 days of age and in all dogs sacrificed at 2 and 4 years of age. Dysplasias included focal aggregates of nuclei in the rod and cone layer, retinal folds, and retinal rosettes. Atrophic changes included altered rosettes, as well as the rest of the retina, loss of rods and cones, and/or thinning of inner and outer nuclear layers. These lesions were bilateral and focal-to-diffuse in nature. They increased in severity with increasing radiation dose. In dogs exposed on ppd 2, central retinal lesions only were seen in 1 of the 20 dogs sacrificed at 70 days of age. No lesions were seen in dogs sacrificed at 2 or 4 years. Central and peripheral retinal lesions were seen in 19 of the 20 dogs and in all dogs sacrificed at 70 days and at 2 or 4 years, respectively.

In summary, ocular effects have been reported in both humans and laboratory animals after radiation doses exceeding 0.6 Gy (60 rad). These effects range from mild opacities of the lens to cataract formation

and alterations in both the posterior chamber of the eye and of the retinal structures. The effects are not immediate, and in people may occur several years after the initial exposure.

#### 3.2.1.8 Dermal Effects

Clinically observable dermal radiation effects ranging from erythema (skin reddening) to necrosis have been observed following external beta, gamma and x ray exposure above threshold doses at high dose rates. A transient erythema, the earliest sign of overexposure of the skin, occurs after a dose of about 300 rad (3 Gy), and was once used by physicians to calibrate x ray machines. The erythema appears several hours after exposure, and disappears within a day. Much greater radiation doses lead to a second erythema several weeks later, which lasts for about a month. Greater doses lead to loss of hair, peeling of the skin (dry desquamation), blistering (wet desquamation), ulceration, and necrosis (Potten 1985). The USNRC limit for occupational exposure of the skin is 50 rem (0.5 Sv) per year is protective for such effects. The skin has a susceptible cell population sensitive to the effects of ionizing radiation. The target cells are those comprising the germinal cells of the skin (stratum germinativum), also known as the basal cell layer, which is itself affected by the thickness of the various skin layers of the epidermis. Normally, the basal cells give rise to the outer layers of the skin (stratum granulosum, stratum lucidum, etc.) and finally form the outmost protective dead layer of the skin, the stratum corneum.

Radiation effects on the skin are proportional to the dose received by this germinal cell layer and to the type of radiation received. Alpha particles with energies greater than 7.5 MeV (8.8 MeV $^{212}$Po in the $^{232}$Th series, 8.8 MeV $^{213}$Po in the $^{241}$Pu series, 7.7 MeV $^{214}$Po in the $^{238}$U series and possibly 7.4 MeV $^{215}$Po in the $^{235}$U series) can penetrate the stratum corneum; therefore, there could be an alpha skin dose in these situations, but much of their energy will be expended in the epidermis, leaving only a small portion for dermal exposure. In general, alpha particles with energies less than 7.5 MeV that deposit on the skin surface (stratum corneum) have little effect, given the short penetration range of this type of radiation. The bulk of the dose is absorbed by the stratum corneum, comprised of dead cells, phospholipids, waxes, and other large complex molecules (Riviere and Spoo 1995). Beta and gamma radiation, which can penetrate deeper to live cell layers, can produce erythema, indicating a vascular component manifested by vasodilation and probably mediated by histamine or other inflammatory mediators. As the dose increases, epilation, dry and/or moist desquamation, and necrosis can occur. The threshold dose of gamma radiation in humans required to produce skin erythema over an area of 10 cm$^2$ is 600–800 rad (6–8 Gy) for single doses and 3,000 rad (30 Gy) for multiple (fractionated) doses (Adams and Wilson 1993). The threshold

dose increases with decreasing area of the irradiated skin. The dermis is less severely affected, given its population of less active cells, connective tissue, sebaceous glands, and nerve fibers. However, the endothelial cells associated with the dermal blood vessels are somewhat more susceptible and may play a role in the production of erythema after receiving doses of ionizing radiation. The long-term effects on the skin after receiving over 1,000 rad (10 Gy) of ionizing radiation include pigmentation, epidermal atrophy, dermal fibrosis, and atrophy of several dermal and epidermal structures, such as sweat and sebaceous glands and hair follicles.

Hahn et al. (1975) reported the effects of ionizing radiation on the skin of Beagle dogs after inhalation exposure to $^{90}$Y in FAP. Four of the 7 dogs exposed to 14–22 mCi (520–814 MBq) initial lung burden (32–40 mCi [1,200–1,500 MBq] whole-body burden) developed a nasal dermatitis. Hobbs et al. (1972) exposed 33 Beagle dogs to initial lung burdens of 3,600, 1,800, 1,200, 780, 400, 210, 110, and 0 μCi (133, 67, 44, 29, 15, 8, 4, and 0 MBq) $^{90}$Y/kg body weight. Patches of radiation alopecia were found on the dorsum of the nose of four animals that died 70–91 days postexposure. These patches were characterized by a thinning of the outer epidermal layer of the skin, atrophy, and loss of hair follicles and hair shafts. Dermal collagen seemed unaffected. Nasal dermatitis, however, is unlikely to occur in humans for two reasons: (1) these animals were exposed to very high activities of $^{90}$Y that are essentially out of the realm of possibility for humans, and (2) these effects are likely to occur in animals with long snouts or muzzles.

Syrian golden (23) and white (24) hamsters (8 weeks of age) were exposed to a $^{85}$Kr source that was in direct contact with the skin. Skin-absorbed doses ranged from 2,000 to 10,000 rad (20–100 Gy) and were delivered at the rate of 495 rad/min (4.95 Gy/min). Within 24 hours after radiation, erythematous reactions developed and persisted for several days postexposure. At sites where larger doses were applied, severe radiation dermatitis developed and sometimes resulted in ulcerative changes in the epidermis. Permanent epilation resulted at doses of 10,000 rad (100 Gy), and doses of 4,000 rad (40 Gy) induced temporary epilation up to the 17th week in all males and most of the females. Growth of grey hair was subsequently observed in the exposed areas of all animals in the 4,000 rad (40 Gy) dose group. Females receiving 2,000 rad (20 Gy) showed about 12 weeks of epilation followed by growth of grey hair in most of them. Some males showed epilation for a short period of time, and the rest of the males showed initial and transient periods of epilation followed by growth of normal hair. Complete epilation occurred in white hamsters receiving 4,000 and 10,000 rad (40 and 100 Gy) and recuperation of hair growth in these animals was not observed. A short period of epilation was observed, followed by growth

of normal hair in animals exposed at the 2,000-rad (20 Gy) level. Few animals showed complete epilation preceded or interrupted by periods of growth of normal hair. No spreading of the hair-greying effect of beta particles was observed in this experiment (Garcia and Shubik 1971).

Similar results were found in pigs, whose skin is considered to be most like that of humans. Hopewell et al. (1986) studied the dose-effect relationship as a function of an irradiated area of the skin by irradiating an area of skin in 3–4 month old large white pigs with $^{90}$Sr, $^{170}$Tm, or $^{147}$Pm disk sources of different diameters. These radionuclides emit beta particles with energies of 0.55, 0.97, and 0.22 MeV that can penetrate 2, 4, and 0.5 mm of tissue, respectively, compared with 0.007 mm for the stratum corneum. The diameter of the sources varied from 1 to 40 mm for $^{90}$Sr, from 0.1 to 19 mm for $^{170}$Tm, and from 2 to 15 mm for $^{147}$Pm. In the porcine model, the $ED_{50}$ values for moist desquamation for $^{90}$Sr varied from 2,750 rad (27.5 Gy) for the 22.5-mm diameter source to 7,500 rad (75 Gy) for the 5-mm source. An increase in source diameter to 40 mm did not significantly change the $ED_{50}$ value from that obtained with a 22.5-mm source. $^{170}$Tm irradiation in the pig produced no distinct area effect for sources 5–19 mm in diameter ($ED_{50}$ for moist desquamation ~8,000 rad [~80 Gy]). Acute tissue necrosis was only achieved in pig skin by very high doses ($ED_{50}$ $14,000 rad [$140 Gy]) from sources #2 mm in diameter. Irradiation of pig skin with $^{147}$Pm produced acute epithelial breakdown but only after high skin-surface doses ($ED_{50}$ 55,000–72,500 rad [550–725 Gy] for 15–2 mm sources). In a similar experiment, Hopewell et al. (1986) exposed SAS/4 randomly-bred male mice, 11–12 weeks old to $^{90}$Sr, $^{170}$Tm, and $^{147}$Pm, again with the sources varying in diameter. $^{90}$Sr and $^{170}$Tm exposure in the mouse resulted in a distinct field-size effect for sources 5–22.5 mm in diameter; the $ED_{50}$ values for moist desquamation were 2,200–2,750 rad (22–27.5 Gy) for the 22.5-mm source and 7,500–9,000 rad for the 5-mm source. There was a distinct source area effect; the $ED_{50}$ values decreased as the source diameter increased. Acute tissue breakdown was only achieved in mouse skin by very high doses ($ED_{50}$ $14,000 rad) from sources of #2 mm in diameter from both types of beta emitters. The large differences in doses required to produce the same effect, with higher energy beta particles producing a greater effect from the same size source by these three radionuclides, may be due to differences in penetrating power. The lower energy beta particles deposit a larger portion of their energy in the dead layers of the stratum corneum, compared with live tissue, so the actual live tissue doses may be larger for the higher energy beta emitters.

A study by Song et al. (1968) examined the efficacy of several anti-inflammatory agents on the suppression of the early increase in radiation-induced vascular permeability to plasma protein in guinea

pigs (radiodermatitis is one limiting factor in radiation therapy because the skin is the first in line for exposure to absorb the energy). Albino male guinea pigs were exposed to 3,000 rep (1 rep . 1 rad) of β particles (750 rad/min [7.5 Gy/min]) from a $^{90}Sr$ /$^{90}Y$ source. Immediately after irradiation, $^{125}I$-labeled guinea pig serum albumin (15 μCi [0.56 MBq] in 0.15–0.20 mL of saline) was injected into the blood. The peak increase in accumulation of vascular permeability as measured by plasma protein between the control and the 3,000-rad (30 Gy) beta-irradiated skin was determined to occur at 18 hours. A significant increase in vascular permeability occurred in the control group receiving no anti-inflammatory drug, as demonstrated by an approximately 3- and 1.6-fold increase in the 18-hour accumulation of plasma protein in the irradiated epidermis and dermis, respectively.

External radiation exposure shows similar results in humans. Birioukov et al. (1993) reported on a case study in which 12 men developed different forms and stages of chronic radiation dermatitis caused by accidental exposure to beta and gamma radiation during and after the Chernobyl nuclear power plant accident. Nine of the men were close enough to the accident to receive doses ranging from 350–550 rad (3.5–5.5 Gy). Three men received doses ranging from 200–350 rad (2–3.5 Gy): two had worked in the contaminated zone for 2 months to 3 years and one was inside the power plant during the accident. All the men were diagnosed with ARS of varying severity after the accident. All the men except one had chronic radiation dermatitis on the upper and lower extremities. The other patient had slight radiation dermatitis on the neck.

Klener et al. (1986) reported another human case study in which a male technician was accidentally irradiated by a sealed 3,000 Ci (110 TBq) $^{60}Co$ telotherapy source that he had been installing. A film dosimeter worn during the accident indicated a dose of 159 rad (1.59 Gy); however, his whole body was highly non-uniformly irradiated. His health status was followed for 11 years after the accident.
Eight days after the accident, he developed severe skin changes on the left hand (reddening and painful inflammation) that would result from doses much greater than 159 rad (1.59 Gy). Clearly, his left hand suffered a very much greater dose than that shown on his film badge. Since he was left-handed, it seems likely that his left hand was closer to the radioactive source and received a much larger dose than his film badge. Apparently, he severely overexposed his left hand during his several unsuccessful attempts and his final successful attempt to place the source back into the container using improvised tools. He also suffered epilation in a small area of the left temporal region, with minor deviations in peripheral blood counts. In the following year, repeated surgery due to secondary skin defects of the left hand resulted in

the loss of the second through fifth fingers; effects included serious trophic changes characterized by a smoothed discolored skin, hard swelling of deep skin layers, and disturbed local blood flow.

In laboratory animal studies, Hulse (1966) exposed albino hairless mice to 750–1,500 rad (7.5–15 Gy) of $^{204}$Tl radiation (0.77 MeV beta particles) to determine if a nonepilating dose produced skin erythema. No visible changes in the skin of albino hairless mice were observed with a 750-rad (7.5 Gy) exposure. Only slight erythema was noted in the 1,500-rad (15 Gy) animal groups. Using slightly higher doses, Etoh et al. (1977) irradiated male albino guinea pigs at a total of 6 sites per animal. Maximum cell loss of recognizable basal cells of 20% on day 8, 60% on day 12, and 75% on day 15 occurred after irradiation with 1,000, 2,200, and 3,000 rad (10, 22, and 30 Gy), respectively. The data for the 5,000-rad (50 Gy) exposure were similar to data for 3,000 rad (30 Gy). Regeneration occurred from survivors within the irradiated area after 1,000 and 2,200 rad (10 and 22 Gy), and was completed in 5 days. No hyperplasia was seen at 1,000 rad (10 Gy), but a long-lived hyperplastic epidermis resulted after the higher doses. Lefaix et al. (1993) exposed large white pigs to a single dose of 12,000, 16,000, or 25,600 rad (120, 160, or 256 Gy) applied to the outer side of the right thigh; in another group, some animals were given single doses of 1,600, 3,200, 4,800, 6,400, 8,000, and 9,600 rad (16, 32, 48, 64, 80, and 96 Gy) applied to the back skin. Data were collected 30 weeks after exposure. No change in the skin surface was observed following a dose of 1,600 rad (16 Gy). After a 3,200-rad (32 Gy) dose, erythema was observed. After 4,800 rad (48 Gy), desquamation of the epidermis developed at the 12th week post-irradiation. At 6,400, 8,000, and 9,600 rad (64, 80, and 96 Gy) all showed a moderate erythema in the first 3–4 days, a distinct erythema after 3–5 weeks, and moist desquamation after 7–12 weeks. Skin necrosis was observed during the 5th week following doses to 12,000 and 16,000 rad (120 and 160 Gy), and cutaneous and muscular ulceration during the 6th week. The highest dose of 25,600 rad (256 Gy) caused skin necrosis at the end of the second week and well-delimited ulceration by the third week. After doses of 12,000, 16,000, and 25,600 rad (120, 160, and 256 Gy), which all induced skin and skeletal muscle ulceration, and 6,400, 8,000, and 9,600 rad doses, which induced dried exudate crusts, damaged skeletal muscles healed by replacement fibrosis and scar formation. It should be noted that the 0.77 MeV $^{204}$Tl beta particles can penetrate 300 mg/cm$^2$ of material, or approximately 0.3 cm of tissue, which is enough to penetrate all layers of the skin and continue to penetrate into the skeletal muscle.

In summary, the skin is resistant to the deterministic effects of radiation until a threshold of 200–300 rad (2–3 Gy) is reached, after which the effects appear to follow a dose-effect relationship (Etoh et al. 1977;

Hulse 1966; Lefaix et al. 1993). Ionizing radiation affects the deep, rapidly multiplying cells of the epidermis (basal cells), which are at a mean depth of 0.007 cm below the outer surface layer of dead cells and which are responsible for the production of the more superficial layers of the epidermis. Other cells within the epidermis that multiply rapidly, such as cells that surround the hair follicle, can also be affected by ionizing radiation, resulting in epilation. Dermal radiation effects seem to be most common after either a direct dermal exposure to a beta or gamma emitter or after external exposure scenarios; alpha emitters, due to their short penetration range, do not penetrate the upper, dead layers of the epidermis (stratum corneum). A clear dose-effect relationship between radiation and skin damage as a whole was demonstrated in humans and in animals. In humans, the earliest response is a mild, transitory erythema that appears several hours after a dose of about 300 rad (3 Gy). Responses ranged from mild epilation that led to the return of normal hair growth at a dose of 2,000 rad (20 Gy), to ulcerative dermatitis and permanent epilation at doses up to 10,000 rad (100 Gy) (Garcia and Shubik 1971). Moist desquamation occurred in pigs at 2,250–7,500 rad (22.5-5.75 Gy) and acute tissue necrosis occurred at doses of 14,000 rad (140 Gy) and above (Hopewell et al. 1986). Erythema and epilation, followed by serious trophic changes and altered skin blood flow, have also been reported in a man whose film badge showed a dose of 159 rad (1.59 Gy); however, the affected areas on the hand received a much higher dose than that reported on the film dosimeter (Klener et al. 1986). Men exposed to external radiation (200–550 rad [2–5.5 Gy]) from the Chernobyl reactor accident also developed chronic dermatitis as a result of the exposures.

Data for dermal and ocular effects in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

#### 3.2.1.9 Genotoxic Effects

The scientific literature contains abundant information on the genotoxic effects of all forms of ionizing radiation from multiple routes of exposure. Tables 3-4 and 3-5 summarize several representative studies that demonstrate the genotoxic end points that can be caused by radiation using *in vivo* and *in vitro* testing systems. However, genetic effects of radiation have never been seen in any human population exposed to any level of radiation.

The data presented in Tables 3-4 and 3-5 show that genotoxicity is a major toxicological end point for exposure to ionizing radiation; specific end points consist of chromosomal aberrations and breaks,

reciprocal translocations, deletions, sister chromatid exchanges, dominant lethal mutations, sperm anomalies, and mutations. DNA is a major target molecule during exposure to radiation (see Chapter 5). Other macromolecules, such as lipids and proteins, are also at risk of damage when exposed to ionizing radiation. The genotoxicity of ionizing radiation is an area of intense study, as damage to the DNA is ultimately responsible for many of the adverse toxicological effects described so far in this chapter. Cells depend on their DNA for coding information to make specific enzymes, proteins, hormones, vasoactive substances, and a host of other essential chemicals. When the genetic information containing the "blueprint" for these substances is disturbed, cellular homeostasis is disrupted, resulting in a wide-range of immediate and/or delayed toxicological effects in a number of organ systems, as described earlier in this chapter. Disruptions and changes of the cellular genome are also thought to be responsible for the formation of cancer in both humans and laboratory animals.

Radiation can interact either directly or indirectly with the cellular DNA to produce the effects seen in Tables 3-4 and 3-5. These interactions can be classified as direct and indirect interactions. In direct interactions with DNA (as well as other macromolecules), an alpha particle, beta particle, or gamma ray knocks an electron out of the DNA molecule through an ionizing collision. This can break the intramolecular chemical bond that contains the vital information that must be transmitted to the daughter cells. Complete repair is normally expected, but if the damage goes unrepaired, the information encoded in the DNA structure is distorted, and faulty information is transmitted to the daughter cells during mitosis, or else the cell dies and terminates the genetic defect. These effects can result in the genetic effects listed in Tables 3-4 and 3-5. In indirect interactions of with DNA, radiation has no direct contact with the DNA; instead it interacts with smaller molecules, especially water, surrounding the DNA to produce highly reactive radicals and ions like those produced in normal metabolic processes, and the end-products of this reaction diffuse away from the site of interaction with the radiation and interact with the DNA, breaking its molecular bonds just as with direct radiation. Misrepair and replication can then produce the adverse effects listed in Tables 3-4 and 3-5. More specific information about how radiation produces its effects on DNA and other macromolecules is presented in Chapter 5 of this profile.

## Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo*

| Species (test system) | End point | Results | Reference | Radionuclide |
|---|---|---|---|---|
| ALPHA PARTICLES | | | | |
| Mammalian cells: | | | | |
| Human peripheral blood lymphocytes | Chromosomal aberrations | + | Pohl-Ruling and Fischer 1979 | [222]Rn (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Sasaki et al. 1987 | [232]Th (I) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Steinstrasser 1981 | [232]Th (I) |
| Monkey peripheral blood lymphocytes | Chromosome aberrations | + | Brooks et al. 1992 | [239]Pu (I) |
| Monkey peripheral blood lymphocytes | Chromosome aberrations | + | LaBauve et al. 1980 | [239]Pu (I) |
| Mouse germ cells (male) | Chromosomal aberrations | + | Beechey et al. 1975 | [239]Pu (I) |
| Mouse germ cells (male) | Chromosome fragmentation | + | Pomerantseva et al. 1989 | [238]Pu (I) |
| Mouse germ cells (male) | Heritable reciprocal translocations | + | Generoso et al. 1985 | [239]Pu (I) |
| Mouse germ cells (male) | Reciprocal translocations | + | Grahn et al. 1983 | [239]Pu (I) |
| Mouse germ cells (male) | Reciprocal translocations | + | Pomerantseva et al. 1989 | [238]Pu (I) |
| Mouse germ cells (male) | Reciprocal translocations | + | Searle et al. 1976 | [238]Pu (I) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Pomerantseva et al. 1989 | [238]Pu (I) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Searle et al. 1976 | [238]Pu (I) |
| Mouse | Sperm abnormalities | + | Beechey et al. 1975 | [239]Pu (I) |
| Mouse | Sperm abnormalities | + | Pomerantseva et al. 1989 | [238]Pu (I) |
| Mouse | Sperm abnormalities | + | Searle et al. 1976 | [238]Pu (I) |
| BETA PARTICLES | | | | |
| Invertebrate animal cells: | | | | |
| *Drosophila melanogaster* (male) | Large deletions | + | Fossett et al. 1994 | HTO: [3]H (I) |
| Plants: | | | | |
| *Brassica campestris* T10 and T151 | Chromosome aberrations | + | Dasgupta 1970 | [32]P, [35]S (E) |
| *Vicia faba* | Chromosome breakage | + | Lazanyi 1965 | [90]Sr-[90]Y (E) |
| *V. faba* | Sister chromatid exchange | – | Kuglik and Slotova 1991 | [3]H (I) |
| *V. faba* | Micronuclei | + | Kuglik and Slotova 1991 | [3]H (I) |

## Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo* (continued)

| Species (test system) | End point | Results | Reference | Radionuclide |
|---|---|---|---|---|
| Mammalian cells: | | | | |
| Mouse liver cells | Chromosome aberrations | + | Brooks et al. 1976 | HTO: [3]H (I) |
| Mouse skin cells | Unscheduled DNA synthesis | + | Ootsuyama and Tanooka 1986 | [90]Sr-[90]Y (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Ramaiya et al. 1994 | [137]Cs (I) |
| Mouse germ cells (male) | Reciprocal translocations | + | Shevchenko et al. 1989 | [131]I (I) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Ramaiya et al. 1994 | [137]Cs (I) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Shevchenko et al. 1989 | [131]I (I) |
| Mouse germ cells (female) | Dominant lethal mutations | + | Zhou et al. 1986 | HTO: [3]H (I) |
| Mouse | Sperm abnormalities | + | Shevchenko et al. 1989 | [131]I (I) |
| GAMMA RAYS: | | | | |
| Plants: | | | | |
| *Vicia faba* | Chromosome breakage | + | Lazanyi 1965 | [60]Co (E) |
| *V. faba* | Sister chromatid exchange | + | Kuglik and Slotova 1991 | [60]Co (E) |
| *V. faba* | Micronuclei | + | Kuglik and Slotova 1991 | [60]Co (E) |
| Mammalian cells: | | | | |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Bigatti et al. 1988 | NS (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Klener et al. 1986 | [60]Co (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Lloyd et al. 1994 | [192]Ir (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Milkovic-Kraus et al. 1992 | [60]Co (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Natarajan et al. 1991 | [137]Cs (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Padovani et al. 1993 | [137]Cs (E&I) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Pohl-Ruling and Fischer 1979 | NS (E) |
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Stavem et al. 1985 | NS (E) |

## Table 3-4. Genotoxicity of Ionizing Radiation *In Vivo* (continued)

| Species (test system) | End point | Results | Reference | Radionuclide |
|---|---|---|---|---|
| Human peripheral blood lymphocytes | Chromosome aberrations | + | Stram et al. 1993 | NS (E) |
| Human bone marrow | Chromosome aberrations | + | Stavem et al. 1985 | NS (E) |
| Chinese hamster liver cells | Metaphase chromosomal aberrations | + | Brooks et al. 1971a, 1971b | [60]Co (E) |
| Mouse bone marrow (maternal) | Chromosome breaks | + | Ricoul and Dutrillaux 1991 | [60]Co (E) |
| Mouse fetal liver cells | Chromosome breaks | + | Ricoul and Dutrillaux 1991 | [60]Co (E) |
| Human peripheral blood lymphocytes | Reciprocal translocations | + | Maes et al. 1993 | NS (E) |
| Monkey germ cells (male) | Reciprocal translocations | + | Tobari et al. 1988 | [137]Cs (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Bayrakova et al. 1987 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | DeLuca et al. 1988 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Gilot-Delhalle et al. 1988 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Grahn and Carnes 1988 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Grahn et al. 1983 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Ramaiya et al. 1994 | [137]Cs (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Searle et al. 1976 | [60]Co (E) |
| Mouse germ cells (male) | Reciprocal translocations | + | Shevchenko et al. 1992 | NS (E) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Ramaiya et al. 1994 | [137]Cs (E) |
| Mouse germ cells (male) | Dominant lethal mutations | + | Searle et al. 1976 | [60]Co (E) |
| Mouse germ cells (female) | Dominant lethal mutations | + | Zhou et al. 1986 | [60]Co (E) |
| Mouse | Sperm abnormalities | + | Grahn and Carnes 1988 | [60]Co (E) |
| Mouse | Sperm abnormalities | + | Searle et al. 1976 | [60]Co (E) |
| Mouse | Sperm abnormalities | + | Shevchenko et al. 1992 | NS (E) |
| Mouse bone marrow | Micronuclei | + | Abraham et al. 1993 | [60]Co (E) |
| Mouse thymocytes | DNA fragmentation | + | Sellins and Cohen 1987 | [60]Co (E) |
| Mouse liver cells | DNA fragmentation | – | Sellins and Cohen 1987 | [60]Co (E) |
| Pig skin fibroblasts | Abnormal karyotypes | + | Sabatier et al. 1992 | [192]Ir (E) |

+ = Positive result; – = Negative result; (E) = External dose, ( I) = Internal dose; HTO = tritiated water.

## Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro*

| Species (test system) | End point | Result | | Reference | Radionuclide |
|---|---|---|---|---|---|
| | | With activation | Without activation | | |
| ALPHA PARTICLES | | | | | |
| Prokaryotic organisms: | | | | | |
| *Escherichia coli* | DNA double-strand breaks | ND | + | Wilkins 1971 | [241]Am |
| *E. coli* | DNA single-strand breaks | ND | + | Wilkins 1971 | [241]Am |
| Mammalian cells: | | | | | |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | DuFrain et al. 1979 | [241]Am |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Fajgelj et al. 1991 | [235]U |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Purrott et al. 1980 | [238]Pu |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Takatsuji and Sasaki 1984 | NS |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Takatsuji et al. 1989 | NS |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Wolff et al. 1991 | [226]Ra |
| Mouse bone marrow | Chromosome aberrations | ND | + | Kadhim et al. 1992 | [238]Pu |
| Mouse 10T1/2, 3T3 cells | Chromosome aberrations | ND | + | Nagasaswa et al. 1990a | [238]Pu |
| Chinese hamster ovary cells, K-1 | Chromosome aberrations | ND | + | Nagasawa et al. 1990b | [238]Pu |
| Human fibroblasts | Chromosome breaks | ND | + | Loucas and Geard 1994 | NS |
| Chinese hamster M3-1 cells | Chromosome damage | ND | + | Welleweerd et al. 1984 | [238]Pu |
| Human AT2BE cells and normal fibroblasts | DNA double-strand breaks | ND | + | Coquerelle et al. 1987 | [241]Am |
| Ehrlich ascites tumor cells | DNA double-strand breaks | ND | + | Blocher 1988 | NS |
| Chinese hamster cells, V79-4 | DNA double-strand breaks | ND | + | Jenner et al. 1993 | [238]Pu |
| Human peripheral blood lymphocytes | Sister chromatid exchange | ND | + | Aghamohammadi et al. 1988 | [238]Pu |
| Mouse 10T1/2, 3T3 cells | Sister chromatid exchange | ND | + | Nagasawa et al. 1990a | [238]Pu |
| Chinese hamster ovary cells, K-1 | Sister chromatid exchange | ND | + | Nagasawa et al. 1990b | [238]Pu |
| Chinese hamster V79 cells | Mutations | ND | + | Thacker 1986 | NS |

## Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro* (continued)

| Species (test system) | End point | Result: With activation | Result: Without activation | Reference | Radionuclide |
|---|---|---|---|---|---|
| BETA PARTICLES | | | | | |
| Eukaryotic organisms: | | | | | |
| Fungi: | | | | | |
| *Saccharomyces cerevisiae* PG-60 | Mitotic recombination | ND | + | Gracheva and Korolev 1974 | [32]P |
| Mammalian cells: | | | | | |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Bocian et al. 1977 | HTO: [3]H |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Ribas et al. 1994 | HTO: [3]H |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Tanaka et al. 1994 | HTO: [3]H |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Vulpis 1984 | HTO: [3]H |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Vulpis and Scarpa 1986 | [90]Sr |
| Human bone marrow cells | Chromosome aberrations | ND | + | Tanaka et al. 1994 | HTO: [3]H |
| Human spermatozoa and zona-free hamster oocytes fertilization system | Chromosome aberrations | ND | + | Kamiguchi et al. 1990 | HTO: [3]H |
| Human spermatozoa | Chromosome aberrations | ND | + | Mikamo et al. 1990, 1991 | HTO: [3]H |
| Human bone marrow cells | Chromatid aberrations | ND | + | Tanaka et al. 1994 | HTO: [3]H |
| Chinese hamster ovary cells | DNA single-strand breaks | ND | + | Cleaver 1977 | [3]H |
| Chinese hamster ovary cells | DNA strand breaks | ND | + | Dikomey and Franzke 1986 | [3]H |
| Human peripheral blood lymphocytes | Sister chromatid exchange | ND | + | Crossen and Morgan 1979 | [3]H |
| Human peripheral blood lymphocytes | Sister chromatid exchange | ND | – | Ribas et al. 1994 | HTO: [3]H |
| Chinese hamster ovary cells | Sister chromatid exchange | ND | + | Roberts et al. 1987 | [3]H |
| GAMMA RAYS | | | | | |
| Prokaryotic organisms: | | | | | |
| *Escherichia coli* K12 | DNA double-strand breaks | ND | + | Krisch et al. 1976 | [125]I |

## Table 3-5. Genotoxicity of Ionizing Radiation *In Vitro* (continued)

| Species (test system) | End point | Result | | Reference | Radionuclide |
|---|---|---|---|---|---|
| | | With activation | Without activation | | |
| Mammalian cells: | | | | | |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Doggett and McKenzie 1983 | [137]Cs |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Fajgelj et al. 1991 | [235]U |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Hintenlang 1993 | [137]Cs |
| Human peripheral blood lymphocytes | Chromosome aberrations | ND | + | Iijima and Morimoto 1991 | [137]Cs |
| Human blood peripheral lymphocytes | Chromosome aberrations | ND | + | Tanaka et al. 1994 | [60]Co |
| Human blood peripheral lymphocytes | Chromosome aberrations | ND | + | Tanaka et al. 1994 | [137]Cs |
| Human blood peripheral lymphocytes | Chromosome aberrations | ND | + | Rueff et al. 1993 | [60]Co |
| Human blood peripheral lymphocytes | Chromosome aberrations | ND | + | Xiao et al. 1989 | NS |
| Human bone marrow cells | Chromosome aberrations | ND | + | Tanaka et al. 1994 | [60]Co |
| Human spermatozoa | Chromosome aberrations | ND | + | Mikamo et al. 1990, 1991 | [137]Cs |
| Human bone marrow cells | Chromatid aberrations | ND | + | Tanaka et al. 1994 | [60]Co |
| Human blood peripheral lymphocytes | DNA strand breaks | ND | + | Rueff et al. 1993 | [60]Co |
| Human lung carcinoma lines (HC12, HX149, HX147A7, HX148G7) | DNA double-strand breaks | ND | + | Cassoni et al. 1992 | [60]Co |
| Human AT2BE cells and normal fibroblasts | DNA double-strand breaks | ND | + | Coquerelle et al. 1987 | [60]Co |
| Mouse (BALB/c, SC3T3/W, Scid/St cells) | DNA double-strand breaks | ND | + | Biedermann et al. 1991 | [137]Cs |
| Chinese hamster cells, V79-4 | DNA double-strand breaks | ND | + | Jenner et al. 1993 | [60]Co |
| Mouse thymocytes | DNA fragmentation | ND | + | Sellins and Cohen 1987 | [60]Co |
| Human peripheral blood lymphocytes | Sister chromatid exchange | ND | – | Iijima and Morimoto 1991 | [137]Cs |
| Human spermatozoa and zona-free hamster oocytes fertilization system | Micronuclei | ND | + | Kamiguchi et al. 1991 | [137]Cs |
| Chinese V79 hamster cells | Mutations | ND | + | Thacker 1986 | [60]Co |

NA = not applicable; ND = no data; – = negative results; + = positive results

The structure of the DNA molecule is damaged after direct or indirect interactions by radiation. Significant amounts of damage to the DNA lead to errors for gene coding of essential enzymes, proteins, and other essential molecules. DNA base-pair damage is the predominant type of DNA damage, followed (in decreasing order of incidence) by single strand breaks (which are four times less prevalent than base-pair lesions), DNA-protein cross-linkages, and double-strand breaks. At the molecular level, an important type of change to DNA that is frequently produced by radiation is the removal of a base, forming an apurinic or apyrimidinic site. The deletion or total destruction of DNA bases, destruction of deoxyribose residues, and deamination of cytosine or adenine are only a few of the many ways radiation can alter the DNA at a molecular level. Minor damage left unrepaired or damage that was not completely or correctly repaired can result in mutations. A more in-depth discussion of the alterations at the DNA level by radiation, including some DNA repair mechanisms, is presented in BEIR V (1990) and in Chapter 5.

Damage to genetic material in an organism may have one of several outcomes. First, enough damage can cause cell death. Second, the genetic material may be repaired by the cell's native DNA repair mechanisms. If the damage is small and the DNA can be repaired correctly prior to cell division, no adverse effects are likely to come from the genetic damage. Chromosomal repair mechanisms have likely existed since life began and our knowledge of these mechanisms has existed for many years. Without these repair mechanisms, the normal damage that occurs to the entire organisms's DNA every day spontaneously, and from other sources such as normal metabolic products, mutagenic chemicals and background radiation, could be lethal. Chromosomal repair mechanisms are a method of minimizing damage, including radiation damage to DNA, providing that the dose of radiation is not so large as to overwhelm them. If the damage is reparable and the cell divides prior to repair, or if the damage is so extensive it cannot be repaired by the normal mechanisms, the cell may die. The results range from no apparent effect on the organs if few or scattered cells die to damaged tissues at higher doses. Another alternative is that the DNA damage is not repaired, the cell lives and carries out its normal functions, and then divides to produce progeny cells. If the progeny cells die, then the mutational event is considered a lethal mutation with no consequences. If the progeny cells live, then the cells will likely carry these genetic mutations forward into all future daughter cells. In-depth reviews of these mutation processes and their impact on the induction of cancer in animals and humans are available (Hoffman 1996; Pitot III and Dragan 1996; Sanders 1983; Sanders and Kathren 1983).

If the cell survives the radiation-induced genetic damage and carries the mutations into future cell populations, two events can take place. First, the cell may carry the DNA defect and express an adverse event, such as altered protein and enzyme synthesis and defects in cellular metabolism. These defects can be numerous, depending largely on where on the genome the mutation takes place and how critical the normal gene is to normal cell function. The second event is multi-stage carcinogenesis, which is discussed in more detail later in Chapter 5.

Both somatic and reproductive cell chromosomes can sustain damage after exposure to radiation. Damage to the human genome in exposed populations of humans has potentially serious implications. If genetic damage occurs in the reproductive cells (sperm and ova), this may result in decreased fertility, malformed fetuses, and certain hereditary diseases. These effects have been observed in animal studies, but long-term follow-up of radiation-exposed human populations has not identified any genetic effects.

Estimates of spontaneous genetic diseases vary. Table 3-6 shows that genetic diseases occur spontaneously (naturally) in approximately 5% of the population (excluding genetic contributions to heart, cancer, and other selected human diseases). UNSCEAR (1993) reported that about 8% of liveborn humans will have a hereditary disease that leads to a serious handicap manifested before 25 years of age. This 8% figure includes all serious congenital anomalies, some of which may be only slightly influenced by transmitted mutations. Before one begins to determine whether human genetic damage can be caused by exposure to increasing doses of radiation, it is necessary to know what the normal, spontaneous, or "background" rates of genetic diseases are in the human population exposed to ambient levels. Several investigators have performed work to measure the spontaneous frequencies of genetic anomalies and spontaneous mutation rates of many genetic traits in humans throughout the world (Childs 1981; Czeizel and Sankaranarayanan 1984; Stevenson 1959, 1961; Stevenson and Kerr 1967). Difficulties are clearly inherent in such comprehensive studies. As an example, as our knowledge of human and animal genetics increases, discrepancies in the data may arise from changes in the classification of some genetic disorders. For example, Stevenson (1959) estimated that 30.7/1000 live births were due to autosomal dominant genetic disorders, while in a study 15 years later by Trimble and Doughty (1974) estimated that only 0.8/1000 live births for the same class of genetic disorders. The data from the Stevenson (1959) data

## Table 3-6. Estimated Genetic Effects of 1 Rem (0.01 Sv) of Radiation per Generation[a]

| | Spontaneous/ not irradiated | Irradiated Additional cases/$10^6$ liveborn offspring/rem (0.01 Sv)/generation | |
|---|---|---|---|
| Type of disorder | Current incidence per million liveborn offspring | First generation | Equilibrium |
| Autosomal dominant [b] | | | |
| Clinically severe | 2,500[c] | 5–20[d] | 25[e] |
| Clinically mild | 7,500[g] | 1–15[d] | 75[e] |
| X-linked | 400 | <1 | <5 |
| Recessive | 2,500 | <1 | Very slow increase |
| Chromosomal | | | |
| Unbalanced translocation | 600[h] | <5 | Very little increase |
| Trisomies | 3,800[i] | <1 | <1 |
| Congenital abnormalities | 20,000–30,000 | 10[j] | 10–100[k] |
| Other disorders of organs [l] | | | |
| Heart [m] | 600,000 | | |
| Cancer | 300,000 | Not estimated | Not estimated |
| Selected others | 300,000 | | |

[a]Risks pertain to average population exposure of 1 rem per generation to a population with the spontaneous genetic burden of humans and a doubling dose for chronic exposure of 100 rem (1 Sv)

[b]Assumes that survival and reproduction are reduced by 20-80% relative to normal (s=0.2-0.8), which is consistent with the range of values in Table 2.2 in BEIR (1990).

[C]Approximates incidence of severe dominant traits in Table 2-2 in BEIR (1990).

[D]Calculated using Equations (2-7) in BEIR (1990) with s=0.2-0.8 for clinically severe and s = 0.01-0.2 for clinically mild.

[e]Calculated using Equations (2-1) in BEIR (1990), with the mutational component = 1.

[f]Assumes that survival and reproduction are reduced by 1-20 percent relative to normal (s=0.01-0.02).

[g]Obtained by subtracting an estimated 2,500 clinically severe dominant traits from an estimated total incidence of dominant traits of 10,000.

[h]Estimated frequency from UNSCEAR (1982, 1986).

[i]Most frequent result of chromosomal nondisjunction among liveborn children. Estimated frequency from UNSCEAR (1982, 1986).

[j]Based on worse-case assumption that mutational component results from dominant genes with an average s of 0.1: hence, using Equation 2.3 in BEIR (1990), excess cases <30,000 x 0.35 x $100^{-1}$ x 0.1 = 10.

[k]Calculated using Equation 2-1 in BEIR (1990), with the mutational component 5-35%.

[l]Lifetime prevalence estimates may vary according to diagnostic criteria and other factors. The values given for heart disease and cancer are round-number approximations for all varieties of the diseases, and the value for other selected traits approximates that for the tabulation in Table 2-4 of BEIR (1990).

[m]No implication is made that any form of heart disease is caused by radiation among exposed individuals. The effect, if any, results from mutations that may be induced by radiation and expressed in later generations, which contribute, along with other genes, to the genetic component of susceptibility. This is analogous to environmental risk factors that contribute to the environmental component of susceptibility. The magnitude of the genetic component in susceptibility to heart disease and other disorders with complex etiologies is unknown.

Source: adapted from BEIR V 1990

set included disorders now known to not be of an autosomal dominant mechanism, resulting in an artificially high estimate in the 1959 report. Definitions of serious and mild genetic disease, size of the population sampled and the specific world location sampled, in addition to the frequencies of some genetic diseases tending to wax and wane over a number of years, will all significantly contribute to the problem of obtaining stable and accurate estimates of background genetic disease burdens in humans.

Table 3-6 summarizes the current incidence of some generalized genetic anomalies (background levels of genetic disease) and the estimated genetic effects of 1 rem (0.01 Sv)/year/generation of radiation on the genome of humans based on an assumed doubling dose of 100 rem (1 Sv) (BEIR V 1990).

Determining the genotoxic effects of ionizing radiation in a population of humans is difficult. Several factors complicate making such predictions of genotoxic effects in humans. First, the genotoxic effects of radiation in humans must be detected in the offspring from the parent(s) that were irradiated.

Given the normally long life cycle of humans compared to laboratory animal models, it may be a few weeks to many years before any genetic effects induced by radiation express themselves in the offspring of an exposed human population. The epidemiologic studies that are needed to accumulate a sufficient database of information after such an exposure would be both time consuming and expensive, with the final results most likely not being available for years after exposure. In addition, radiation effects in an exposed population may vary significantly by exposure location: all of the population may not have received a uniform whole body dose, and different individuals would have received different radiation doses, thus complicating the data collection process. Distance-from-exposure source and total organ dose received are only estimates and not a precise measurement. Age and sex distribution of the exposed population and their normal probabilities of producing children must also be accounted for and determined using relevant control populations.

A major problem with the genetic studies on humans relates to the many remaining uncertainties about dosimetry. Many of the difficulties described above were encountered with the data collected from the exposures to radiation resulting from the atomic bombing at Hiroshima and Nagasaki, Japan; these exposures consisted primarily of external gamma radiation. The original dosimetry measurements from that exposure (T65D) have been revised (DS86) and are still undergoing revision to more accurately ]

determine the actual doses of radiation received by individuals who survived the atomic bomb explosions in August 1945. Although no increased incidence of hereditary effects among the children and grandchildren of the atomic bombing survivors has been seen, certain authors and committees made certain assumptions about the induction of radiation-induced hereditary effects and have calculated the chances of the occurrence of these effects; the results and assumptions are presented and discussed in other texts (BEIR IV 1988; BEIR V 1990; UNSCEAR 1993). Another major problem in quantifying genetic effects is the wide spectrum of possible health outcomes that may be attributable to genotoxic events. The total genetic detriment includes health effects that may have minor or insignificant impact, major genetic diseases, and death. Some of these outcomes may be very difficult to measure.

Today, two basic models are used to estimate the risk for radiation-induced hereditary disease for low doses of radiation. These models are the Direct Method and the Doubling Dose Method. Both models are linear, no-threshold models for dose response.

In the Direct Method, the dose-related rate of hereditary effects in mice is extrapolated to humans. However, because of the many uncertainties in this extrapolation, this method is not favored for estimating the chances of a radiation-based hereditary effect in humans.

The Doubling Dose Method requires fewer assumptions and estimates than the direct method. The "doubling dose" of radiation is defined as the dose that induces a mutation frequency equal to the total spontaneous mutation frequency per generation. Hence, the doubling dose of radiation doubles the total mutation frequency per generation. In other words, the dose of radiation to the gonads (testes or ovaries) that, if delivered per generation to all members of a population would, at equilibrium after many generations, doubles the spontaneous burden that existed before exposure began (BEIR V 1990; Faw and Shultis 1993). This method uses the natural frequency of human hereditary disease in determining an estimate of the increased frequency of genetic alterations as a result of a sudden increase in radiation exposure to the general public. Compared to the direct method, the doubling dose method directly takes into account the effect of a genetic anomaly on all generations beyond the first generation. The problem of species extrapolation from animal to human is also somewhat circumvented; in theory, this method

relies entirely on a known estimate of a specific genetic mutation frequency in the human, although some of the doubling-dose estimates originate from data collected in the mouse animal model. Risk estimates of genetic disease using the doubling dose method have been adopted by the latest BEIR committee; however, UNSCEAR still relies on the direct method of risk estimation.

Risk estimates have been reported for humans exposed to radiation, despite the difficulties with the availability of data. Using the epidemiological data gathered after the atomic bombing of Hiroshima and Nagasaki in August 1945, which encompasses nearly 50 years of data, together with data from studies with mice, some estimates of genetic disease risk using the doubling dose method can be derived for human exposures to radiation. These estimates are presented in Table 3-7.

**Table 3-7. Estimated Lower 95% Confidence Limits of Doubling Dose (in rem) from Chronic Radiation Exposure for Malformations, Stillbirths, Neonatal Deaths, and All Untoward Pregnancy Outcomes (Based on the Hiroshima and Nagasaki Atomic Bombing Data)**

| Group | Malformations | Stillbirths | Neonatal death | All untoward outcomes |
|---|---|---|---|---|
| All groups | 96 | 124 | 90 | 60 |
| Only mother exposed | 277 | 32 | 23 | 29 |
| Only father exposed | 65 | 344 | 56 | 41 |
| Combined | 119 | 64 | 35 | 36 |
| Both mother and father exposed | 41 | 73 | 75 | 37 |

Source: adapted from BEIR V 1990 and Schull et al. 1981

NOTE: Data are the lower 95% confident limits of the doubling dose adjusted for concomitant sources of variation. For acute doubling doses, divide by 3. For all estimates adjusted for concomitant sources of variation, the range of the doubling dose is 23–344 rem (0.23–3.44 Sv), the median is 62 rem (0.62 Sv), and the mean is 86 rem (0.86 Sv).

Table 3-7 provides the lower 95% confidence limits of the minimum doubling dose estimates (in rem) on adjusted data from those individuals that survived the atomic blasts of 1945, and are for chronic radiation exposures only. The human data set closely approximates the median values obtained in mice (data not shown), and overall may suggest that humans are somewhat more radioresistant than mice, implying lower risk. Due to the data restrictions in this human population (discussed previously in this section), the human data may be biased in such a way as to yield an artificially lower number than that obtained using

the mouse data. The numbers in Table 3-6 are based on the application of actual doses to models derived from animal experiments. In the case of the survivors of the atomic bombing, Dr. J.V. Neel, who had been studying the genetic effects of these bombings since 1946, concluded that "the children of the most highly irradiated population in the world's history provide no statistically significant evidence that mutations were produced in their parents. . . . In particular, the studies should prove reassurance to that considerable group of exposed Japanese and their children, without whose magnificent cooperation these studies would have been impossible and who over the years have been subject to a barrage of exaggerations concerning the genetic risks involved" (Neel et al. 1990). In short, Neel and others believe that humans may be less sensitive to induction of mutations than mice. The data of Neel and colleagues indicated that mice may be much less sensitive than has been thought, however, to reach this conclusion they had to disregard the genes that have been studied the most (the specific-locus data), based on the argument that those genes might be atypically mutable.

In summary, the intracellular genetic materials in humans and in animals may be damaged by radiation. The severity of these lesions depends on the dose and type of ionizing radiation received and the extent to which these lesions can be repaired by the resident cellular repair systems. These lesions range from point mutations, which cause serious hereditary diseases, and chromosomal aberrations and breaks to lethal mutations of the genetic material, which lead to cellular death.

The amount of radiation needed to cause hereditary effects is not known, because hereditary effects have not been detected in humans. As stated in the UNSCEAR (1993) report, "Epidemiology has not detected hereditary effects of radiation in humans with a statistically significant degree of confidence. The risk estimate based on animals is so small that it would have been surprising to find a statistically significant effect in the end-points studied in Hiroshima and Nagasaki. . . . Risk estimation therefore rests on genetic experimentation with a wide range of organisms and on cellular studies, with limited support from the negative human findings." The two models that currently exist for making these determinations have both strengths and weaknesses. One of the weaknesses is the high rate of spontaneous chromosomal breaks; about 200,000 broken chromosomes are repaired per hour. The main difficultly with estimating genetic effects of radiation is that the frequency of the postulated effects, even for high radiation doses, is less than the annual statistical variability in the number of these that occur spontaneously.

### 3.2.2 Children's Susceptibility

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure.

With respect to chemical toxicity, children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects from environmental insults, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular

enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996).

According to the Law of Bergonie and Tribondeau, rapidly dividing and undifferentiated cells are more sensitive to radiation damage than slowly dividing and highly differentiated cells. This applies to fetal cells as their sensitivity changes with level of activity during the different stages of development, and to all types of radiation whether the dose is delivered internally or externally. Gamma and x rays from sources such as $^{60}$Co and x ray machines are the radiation types with enough penetrating power to externally expose the fetus while *in utero*; alpha and beta emitters, such as $^{239}$Pu and $^{90}$Sr which preferentially distribute to fetal bone, must be internalized by the fetus to cause a radiation dose. The specific organ systems are expected to be the most sensitive to radiation damage during that system's primary period(s) of organogenesis. Prenatally injured cells that replicate while damaged may affect the individual as a child and as an adult. Exposure to radiation after birth results in similar effects in children and adults.

Radiation damage to the fetus thus depends on the dose and type of radiation that delivered it, and the sensitivities of the various organ systems during exposure. The expression of that damage will depend on the efficiency of the fetal repair system that all humans use for protection against low-level radiation to which all life is exposed. External radiation dose depends on the radiation dose rate which would exist if the mother and fetus were not present, the time of exposure, and the shielding which the mother's body and fluids provide the fetus. Natural terrestrial, cosmic, and internal radiation will normally represent the largest radiation dose to the fetus. This can be supplemented by external radiation doses from x ray and nuclear medicine procedures to the mother and any gamma radiation field from sources around the mother, such as radioactive fallout and any nearby radioactive sources. Terrestrial and cosmic radiation doses are affected by the concentrations of various radioactive materials in the surrounding environment, such as soil and construction material, and the altitude, which affects cosmic ray intensity. Internal radiation dose depends on the combination of gamma dose rate to the fetus from radionuclides inside the mother, plus the dose equivalent rate from alpha, beta, and gamma emitting radioactive materials which have entered and distributed within the fetus. Potassium-40, which is the inseparable radioactive component of natural, biologically important potassium, will probably cause the largest portion of the internal dose, but the dose from radon transformation products which cause the largest adult dose will be

minimally important in the fetus because it doesn't breathe. Absorption, distribution, metabolism (if any), and excretion of radionuclides depend largely on the pharmaco/toxicokinetics for both mother and fetus. If the mother can metabolize and excrete the radioactive compound prior to distribution to the fetal compartment, the dose to the fetus is minimized. Those compounds that are easily absorbed and freely distributed to the fetal and/or placental compartments may give a larger dose than those that have low absorption coefficients or those that never leave the maternal blood supply to penetrate peripheral tissues. Compounds that distribute to the fetal compartment and undergo little metabolism and excretion (i.e., extended fetal compartment residence times) are also more likely to cause damage to fetal tissues. The overall dose equivalent, which considers all radiation doses and the quality factors of the radiation, and the dose rate are the major players in predicting fetal toxicity.

Some of the fetal effects which have been observed in humans include mental retardation, IQ reduction, and microencephaly. The pivotal study that links the effects of external radiation to defects in child development is the study conducted by Schull et al. (1988) that describes decreases in IQ scores with increasing maternal doses of ionizing radiation. That study evaluated the quantitative effect of exposure to ionizing radiation on the developing fetal and embryonic human brain after the Hiroshima/Nagasaki atomic bombings of 1945. The sample included virtually all prenatally exposed individuals who received tissue-absorbed doses of 0.50 Gy (50 rad) or more, and many more individuals in the dose range 0–0.49 Gy (0–49 rad) than in the clinical sample. The clinical sample does not include children prenatally exposed at distances between 2,000–2,999 m in Hiroshima and Nagasaki. No evidence of radiation-related effect on intelligence was observed among individuals exposed within 0–7 weeks after fertilization or in the 26th or subsequent weeks. The highest risk of radiation damage to the embryonic and fetal brain occurs 8–15 weeks after fertilization under both the T65D individual specific dosimetric system, developed using data accumulated through 1965 and atomic bomb radiation data from tests in arid climates, and the DS86 system, which accounts for neutron dose reduction from the high ambient relative humidity in Japan during the 1945 blasts. The regression of intelligence score on estimated fetal absorbed dose was linear or linear-quadratic for the group exposed 8–15 weeks after fertilization and possibly linear for the 16–25 week group. The cumulative distribution of test scores suggested a progressive shift downwards in individual scores with increasing dose. The mean IQ scores decreased

significantly and systematically with uterine or fetal tissue dose within the groups exposed during 8–15 and 16–25 weeks postgestation. This effect was not reversible and was the basis for the acute duration MRL.

### 3.2.3 Carcinogenic Effects from Ionizing Radiation Exposure

#### 3.2.3.1 Introduction

Cancer is the major latent harmful effect produced by ionizing radiation and the one that most people exposed to radiation are concerned about. The ability of alpha, beta, and gamma radiation to produce cancer in virtually every tissue and organ in laboratory animals has been well-demonstrated. There is also a large database that exists for people exposed to radiation for diagnostic purposes, those treated for disease with radiation, occupational exposure populations, people that live in high background regions, survivors of radiation accidents, and nuclear bombing survivors. It is presently not clear whether humans are more or less sensitive to the adverse effects of low-levels of radiation than are the laboratory animal models.

The development of cancer is not an immediate effect. It may take several years to develop (referred to as the latent period or latency), if it develops at all. Radiation-induced cancers are the same types that are normally found in an unexposed individual. However, after exposure to radiation, these cancer types may occur with some increasing frequency and therefore can be detected only by epidemiological means. Most of these cancers occur only when those individuals reach an age when these cancers would normally be expected to develop (except for leukemia). For example, a female #10 years of age who was exposed to external radiation from the atomic blast, who survived the acute effects of the initial radiation exposure, would have an increased probability of developing breast cancer as a result of that exposure, but not before the end of the latent period for this specific cancer. The same would be true for the other types of cancers. Radiation-induced leukemia has the shortest latent period at 2 years, while other radiation induced cancers have latent periods >20 years. Radiation carcinogenesis has not been demonstrated in several types of human cells, possibly because the latent period exceeds the human lifespan. Raabe (1994) has developed two- and three-dimensional models of risk of developing cancer as a function of isotope and dose rate. The typical plot of lifespan vs. daily dose rate has three portions based on the cause of death, natural life-span, cancer, and acute radiation syndrome. According to Raabe, at low dose rates the animal's natural life-span is the cause of death before cancer can develop. As the daily

dose rate increases, a threshold is reached where cancer deaths dominate in a dose-responsive manner. Similarly, at high dose rates, a threshold is reached where acute radiation syndrome is the cause of death. These are lifetime studies involving a wide range of dose rates from very high down toward levels that humans may normally experience.

The mechanism by which cancer is induced in living cells is complex and is a topic of intense study. The accepted theory states that the induction of cancer by exposure to radiation takes place in three steps. The first step is initiation, which is a mutational event caused by the effect of the radiation interacting with the cellular genome. This may involve a single gene or multiple genes on one or many chromosomes, and may involve the activation of an oncogene or the mutation and subsequent inactivation of tumor suppressor genes. The mechanism may stall at this point, with the gene(s) either undergoing repair or remaining mutated and dormant. If repair fails to take place at all, if the repair is unsuccessful, or if cell division occurs before repair is complete, and the cell remains viable through future cell generations, the gene(s) appear in the progeny cells and will then enter into the stage of promotion. The second step, promotion, is generally thought to be unrelated to the dose of radiation (initiation step) received, even though thyroid cancer in children from $^{131}I$ or external exposure may suggest otherwise; therefore, the latent period is clearly independent of the initial dose of radiation received. This would be a reasonable explanation of why cancers develop at the ages that they would normally develop in unexposed populations, with the increased incidence of cancer related to the increased number of cell insults/injuries in the genome of the damaged cells. Several promotor agents have been identified, with some acting as both initiators and promotors. In the third step, cell transformation and proliferation, neoplasic cells are produced. More information on how radiation interacts with the genome and on the mechanisms by which it induces cancer is presented in Chapter 5 of this profile.

A few human studies are available that describe the incidences and types of cancers produced by some radionuclides. Osteogenic sarcomas were found in people whose average skeletal doses exceeded 1,380 rad (13.8 Gy) of alpha radiation following exposure to $^{226}Ra$ and $^{228}Ra$ via several routes of exposure (Aub et al. 1952; Evans 1966; Martland 1931; Rowland et al. 1978; Woodard 1980). $^{224}Ra$, used in the treatment of ankylosing spondylitis, has also been implicated in producing osteosarcomas (Chemelevsky 1986; Mays 1988; Spiess and Mays 1970, 1973; Wick et al. 1986). One of the largest cohort of humans available for studying the effects of external radiation and cancer is the group of people exposed to the varying doses of radiation produced by the two atomic bombs detonated in Japan in August 1945. In this

population, an increase in leukemia incidence rate was seen only in those persons whose dose exceeded 10 rad (0.1 Gy). An increased incidence of solid tumors was seen only in those whose dose exceeded 40 rad (0.4 Gy).

Exposure to radiation can produce cancer at any site within the body; however, some sites appear to be more common than others. The BEIR V (1990) committee report came to some conclusions about which sites are more at risk than others in humans, and these data are summarized in Table 3-8. The relative risk of death normalized to a dose of 100 rad (1 Gy) from several types of cancer among 75, 991 atomic bomb survivors whose radiation doses are known are given in Table 3-9.

The conclusions of the BEIR V (1990) report were based on many human epidemiological studies over the past 70–80 years. Laboratory animal data have also proven useful for understanding human risks from radiation, particularly to the respiratory tract of humans, and were included when relevant. The use of human epidemiological data is certainly a valuable tool in determining the long-term carcinogenic effects from radiation. The BEIR V (1990) committee used human epidemiological data whenever possible; however, it also recognized its many limitations when attempting to draw conclusions about the carcinogenic effects of low doses of radiation. No increase in cancer has been observed at low doses. Therefore, for purposes of setting safety standards and public policy, we resort to mathematical models with a postulated zero threshold.

Most of the literature examined reported the effects of radiation in laboratory animal species, such as monkeys, dogs, rats, pigs, mice, and guinea pigs. The short- and long-term effects of radiation in these animals as a result of this research have been studied. When the laboratory animal data are examined more closely, the researcher and risk assessor are faced with a difficult and complex question: “Is this what happens when humans are exposed to this dose of ionizing radiation?” The answer will likely depend on a number of variables, including the toxicological end point being examined (in this case, cancer). The use of human subjects in scientific research is a highly regulated area and, for obvious moral reasons, is not an acceptable practice in the area of radiation biology unless there is full informed consent and the radiation doses are low. This normally leaves radiation biology risk assessors with the following sources of information from which to determine the risks associated with radiation exposure in humans: (1) extrapolation of data from laboratory animal models (which is associated with many uncertainty

**Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation**

| Organ or system | BEIR Committee conclusions about risk | Cancer Relative Risk (RR) Factors (low dose/low dose rate) per $10^6$ rad ($10^4$ Gy) [a] |
|---|---|---|
| Mammary/breast | 1. The development of cancer from susceptible mammary cells due to exposure to ionizing radiation depends on the hormonal status of these cells.<br>2. The age-distribution of radiogenic breast cancers and those breast cancers from unknown causes is similar.<br>3. Women irradiated at #20 years of age are at higher risk than those irradiated later in life.<br>4. There is no evidence to suggest that radiogenic breast cancer will appear during the first 10 years after exposure to ionizing radiation. Peak incidences occur 15 to 20 years after exposure.<br>5. The data show little if any decrease in the yield of tumors when multiple radiation doses are compared to single, brief exposures to ionizing radiation. | 92.5 |
| Lung | 1. Absolute risk of lung cancer from exposure to ionizing radiation is similar for both males and females.<br>2. The data suggest that smoking has a “greater than additive” effect on the development of lung cancer after exposure to ionizing radiation. | 75.4 |
| Stomach/digestive system | 1. The incidence of stomach cancers increases with increased exposure to ionizing radiation.<br>2. Females are at greater risk for developing cancers than are males<br>3. The relative risk for developing cancer is higher for those exposed when 30 years of age or younger.<br>4. The baseline risk for digestive cancers increases with age; most of the excess cancers occur after middle age. | 49.3 |
| Thyroid | 1. Susceptibility to radiation-induced thyroid cancer is greater in childhood.<br>2. Development of thyroid cancer is dependant on the hormonal status of the individual; sustained levels of TSH increase the risk of developing thyroid cancer.<br>3. For those exposed before puberty, the tumors do not appear until after sexual maturation. The risk is greatest for children exposed within the first 5 years of life.<br>4. Females are 2–3 times more susceptible than males to radiogenic (and spontaneous) thyroid cancer.<br>5. Radiogenic cancer of the thyroid is usually preceded by benign thyroid nodules and the frequency of hypothyroidism and goiter is increased in those exposed to large doses when very young. | 32.1 |
| Esophagus | 1. Increased incidences of cancer of the esophagus have been observed to occur in humans receiving doses of ionizing radiation.<br>2. Little human data are available to make strong conclusions about the risk of developing esophageal cancer after exposure to ionizing radiation, although a risk estimate is available. | 9.5 |

**Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)**

| Organ or system | BEIR Committee conclusions about risk | Cancer Relative Risk (RR) Factors (low dose/low dose rate) per $10^6$ rad ($10^4$ Gy) [a] |
|---|---|---|
| Small intestine (duodenum, jejunum, ileum) | 1. Cancers of the small intestine have been produced in laboratory animals exposed to large doses of ionizing radiation.<br>2. None of the human epidemiological studies have conclusively demonstrated an increased risk of developing cancers of the small intestine after exposure to ionizing radiation. | NR |
| Large intestine (colon/rectum) | 1. Data imply that there is an increased risk of developing either colon or rectal cancer after exposure to ionizing radiation<br>2. Based on human exposure data, the development of colon or rectal cancer is not apparent until 15 years after exposure or longer. | 178.5 |
| Skeleton | 1. Large doses of low-LET ionizing radiation can result in the development of bone cancers.<br>2. The data suggest a threshold of between 4 Gy of low-LET or 13.8 Gy of high-LET radiation before increased bone cancers begin to occur. | 1.3 |
| Brain/central nervous system (CNS) | 1. Increased incidences of CNS tumors have been observed in both humans and laboratory animals exposed to ionizing radiation.<br>2. Tumors are both malignant and benign.<br>3. The brain is considered to be relatively sensitive to developing cancer after exposure to ionizing radiation.<br>4. Increases have been reported when irradiated during childhood at doses less than 1–2 Gy. | NR |
| Ovary and uterus | 1. There is no clear relationship between exposure to ionizing radiation and the development of uterine or ovarian cancers | 23.8 |
| Testis | 1. There are few human data available for studying the relationship between exposure to ionizing radiation and testicular cancer.<br>2. The existing data suggest that the testis is relatively insensitive to the carcinogenic effects of ionizing radiation. | NR |
| Prostate | 1. There is a weak association between cancer of the prostate and exposure to ionizing radiation.<br>2. The relative risk of cancer of the prostate due to exposure to ionizing radiation is small. | NR |
| Urinary tract | 1. Exposure to ionizing radiation can cause cancer of the bladder, as well as cancers of the kidney and other urinary structures.<br>2. Women < 55 years old at the time of exposure are at greater risk than older women, with this risk increasing with time after exposure.<br>3. Gender appears to have little effect on the incidence of bladder cancer mortality. | 49.7 |

**Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)**

| Organ or system | BEIR Committee conclusions about risk | Cancer Relative Risk (RR) Factors (low dose/low dose rate) per $10^6$ rad ($10^4$ Gy) [a] |
|---|---|---|
| Parathyroid glands | 1. Increased incidences of hyperparathyroidism, parathyroid hyperplasia and parathyroid adenoma occur after exposure to ionizing radiation.<br>2. The data suggest that the incidences of hyperparathyroidism and parathyroid neoplasia increase with increasing doses of ionizing radiation.<br>3. Time to diagnosis normally is $30 years. | NR |
| Nasal cavity and sinuses | 1. Little human data is available for analysis. Nasal and sinus tumors have been noted after human exposure to internally deposited $^{226}$Ra and $^{232}$Th.<br>2. The latency of these tumors is at least 10 years.<br>3. The risk of developing nasal and sinus cavity tumors from routes other than from internalized sources of alpha ion radiation are extremely low. | NR |
| Skin | 1. Increased incidences of basal cell and squamous cell carcinomas of the skin have been reported after occupational and therapeutic exposures to ionizing radiation.<br>2. Incidence from radiation exposure may be 5 times greater if the skin is also exposed to sunlight | 1.0 |
| Bone marrow (leukemia, lymphoma, and multiple myeloma) | 1. Examples include multiple myeloma, non-Hodgkins lymphoma, and chronic lymphocytic leukemia.<br>2. Multiple myelomas are observed to form after irradiation of the bone marrow.<br>3. The latent period for multiple myeloma is considerably longer than that of leukemia.<br>4. In Japanese A-bomb survivors, an excess of multiple myeloma cases did not appear until 20 years after exposure.<br>5. Excess mortality from multiple myelomas has been observed at doses as low as 0.5-0.99 Gy<br>6. No other form for lymphoma has been consistently observed in human populations exposed to excess amounts of ionizing radiation. | NR |

**Table 3-8. Summary of Risks of Developing Cancer After Exposure to Ionizing Radiation (continued)**

| Organ or system | BEIR Committee conclusions about risk | Cancer Relative Risk (RR) Factors (low dose/low dose rate) per $10^6$ rad ($10^4$ Gy) [a] |
|---|---|---|
| Pharynx, hypopharynx, and larynx | 1. Increased incidences of cancer do arise in these tissues after therapeutic radiation (i.e., ankylosing spondylitis) in the 30–60 Gy range. Increases in these cancers were not statistically significant at the $p<0.05$ level.<br>2. There were no increases in the incidences of these cancers in the Japanese A-bomb survivors exposed to <1 Gy.<br>3. The risk of developing cancers of these tissues after exposure to ionizing radiation appears to be very low. | NR |
| Salivary gland | 1. The incidence of salivary gland tumors was increased in the Japanese A-bomb survivors, patients treated with x rays to the head and neck during childhood, and women treated with $^{131}$I when middle-aged.<br>2. Increases in salivary gland neoplasia are dose-dependent in the Japanese A-bomb survivors, but with no detectable increases in excess mortality.<br>3. The salivary gland appears to be particularly susceptible to the development of cancer after exposure to ionizing radiation. | NR |
| Pancreas | 1. An association between cancer of the pancreas and exposure to ionizing radiation has been suggested in some literature reports.<br>2. Pancreatic cancer has been found in occupationally exposed thorium workers. [b]<br>2. The existing data suggest that the pancreas is relatively insensitive to the carcinogenic effects of ionizing radiation. | NR |

[a] Values from EPA Report 402-R-96-016, Radiation Exposure and Risk Assessment Manual, June 1996. Sum of all values = 760.6, including a remainder incidence risk of 173.4 for all other organs, including those listed in column 3 as NR.

[b] Polednak et al. (1980), *Health Physics* 44 (Suppl 1): 239-251.

Source: summarized from BEIR V 1990

LET = linear energy transport; NR = RR factor not reported.

## Table 3-9. Summary of Radiation Dose Response for Cancer Mortality by Site[a,b]

| Site of cancer | Number of deaths | Statistical p test[c] | Estimated relative risk at 1 Gy (100 rad) | Excess risk per $10^4$ person-year Gy (PY Gy) (per $10^6$ PY-rad) | Attributable risk (%)[d] |
|---|---|---|---|---|---|
| All malignant neoplasms | 5936 | 0.0000 | 1.39 (1.23, 1.46) | 10.0 (8.36, 11.8) | 10.2 (8.50, 12.0) |
| Leukemia | 202 | 0.0000 | 4.92 (3.89, 6.40) | 2.29 (1.89, 2.73) | 55.4 (45.7, 66.3) |
| All cancers except leukemia | 5734 | 0.0000 | 1.29 (1.23, 1.36) | 7.41 (5.83, 9.08) | 7.86 (6.19, 9.64) |
| Digestive organs and peritoneum | 3129 | 0.0000 | 1.24 (1.16, 1.33) | 3.39 (2.27, 4.59) | 6.58 (4.41, 8.91) |
| Esophagus | 176 | 0.02 | 1.43 (1.09, 1.91) | 0.34 (0.08, 0.67) | 12.7 (2.92, 25.0) |
| Stomach | 2007 | 0.0000 | 1.23 (1.13, 1.34) | 2.07 (1.19, 3.05) | 6.26 (3.61, 9.23) |
| Colon | 232 | 0.0000 | 1.56 (1.25, 1.98) | 0.56 (0.26, 0.91) | 15.1 (6.96, 24.7) |
| Rectum | 216 | 0.67 | 0.93 ( , 1.27)[†] | -0.07 ( , 0.25)[†] | -1.93 ( , 7.12)[†] |
| Liver (primary) | 77 | 0.57 | 1.12 (0.87, 1.70) | 0.05 (-0.05, 0.25) | 3.90 (-4.38, 20.5) |
| Gallbladder and bile ducts | 149 | 0.13 | 1.37 (0.98, 1.96) | 0.22 (-0.01, 0.53) | 8.24 (-0.55, 19.5) |
| Pancreas | 191 | 0.53 | 0.89 ( , 1.23)[†] | -0.10 ( , 0.20)[†] | -3.01 ( , 6.21)[†] |
| Other (unspecified) | 81 | 0.29 | 1.32 (0.87, 2.14) | 0.11 (-0.05, 0.35) | 7.73 (-3.29, 24.2) |
| Respiratory system | 747 | 0.0000 | 1.40 (1.21, 1.63) | 1.29 (0.71, 1.96) | 10.1 (5.50, 15.3) |
| Lung | 638 | 0.0000 | 1.46 (1.25, 1.72) | 1.25 (0.70, 1.89) | 11.4 (6.36, 17.1) |
| Breast (female) | 155 | 0.0000 | 2.00 (1.48, 2.75) | 1.02 (0.53, 1.60) | 22.1 (11.4, 34.8) |
| Cervix uteri and uterus (female) | 382 | 0.08 | 1.22 (1.01, 1.50) | 0.60 (0.04, 1.29) | 5.30 (0.34, 11.5) |
| Cervix uteri (female) | 90 | 0.17 | 1.43 (0.93, 2.30) | 0.26 (-0.04, 0.70) | 10.0 (-1.68, 26.9) |
| Ovary (female) | 82 | 0.03 | 1.81 (1.16, 2.89) | 0.45 (0.10, 0.90) | 18.7 (3.97, 37.7) |
| Prostate (male) | 52 | 0.85 | 1.05 ( , 1.73)[†] | 0.03 ( , 0.40)[†] | 1.89 ( , 24.8)[†] |
| Urinary tract | 133 | 0.0000 | 2.02 (1.45, 2.87) | 0.55 (0.26, 0.89) | 22.7 (10.8, 37.1) |
| Malignant lymphoma | 110 | 0.81 | 1.92 ( , 1.40)[†] | -0.02 ( , 0.18)[†] | -1.75 ( , 13.6)[†] |
| Multiple myeloma | 36 | 0.002 | 2.86 (1.55, 5.41) | 0.21 (0.07, 0.39) | 32.5 (11.3, 59.5) |
| Liver (including not specified as primary) | 590 | 0.02 | 1.24 (1.06, 1.47) | 0.63 (0.07, 1.18) | 7.02 (1.87, 13.2) |
| Kidney | 38 | 0.18 | 1.58 (0.91, 2.94) | 0.09 (-0.02, 0.26) | 15.7 (-2.77, 43.3) |
| Bladder | 90 | 0.003 | 2.13 (1.40, 3.28) | 0.41 (0.16, 0.70) | 23.6 (9.31, 40.8) |
| Tongue | 26 | 0.40 | 0.83 ( , 1.49)[†] | -0.02 ( , 0.06)[†] | -5.35 ( , 14.1)[†] |
| Pharynx | 23 | 0.61 | 0.83 ( , 2.04)[†] | -0.02 ( , 0.09)[†] | -6.14 ( , 31.6)[†] |
| Nose | 44 | 0.58 | 0.84 ( , 1.67)[†] | -0.03 ( , 0.12)[†] | -4.04 ( , 14.5)[†] |
| Larynx | 46 | 0.16 | 1.51 (0.95, 2.68) | 0.10 (-0.01, 0.29) | 13.4 (-1.47, 37.1) |

**Table 3-9. Summary of Radiation Dose Response for Cancer Mortality by Site[a,b] (continued)**

| Site of cancer | Number of deaths | Statistical p test[c] | Estimated relative risk at 1 Gy (100 rad) | Excess risk per $10^4$ person-year Gy (PY Gy) (per $10^6$ PY-rad) | Attributable risk (%)[d] |
|---|---|---|---|---|---|
| Skin (except melanoma) | 21 | 0.69 | 1.17 ( , 2.47)† | 0.02 ( , 0.12)† | 5.60 ( , 38.7)† |
| Bone | 27 | 0.65 | 1.22 ( , 2.79)† | 0.02 ( , 0.16)† | 6.56 ( , 42.9)† |
| Brain tumors | 47 | 0.97 | 1.03 (0.51, 2.09) | 0.01 (-0.12, 0.20) | 1.0 (-13.0, 22.5) |
| Tumors of central nervous system (except brain) | 14 | 0.08 | 3.09 (1.06, 9.74) | 0.10 (0.00, 0.24) | 35.9 (1.4, 82.2) |
| Other | 907 | 0.03 | 1.20 (1.05, 1.38) | 0.77 (0.19, 1.44) | 5.65 (1.37, 10.5) |

[a] Adapted from Shimizu et al. 1988. Number in parentheses indicate 90% confidence intervals.
[b] Data includes Hiroshima and Nagasaki, Japan, both sexes (unless specifically otherwise stated), all ages at time of bombing (ATB), from 1950 to 1985.
[c] p-value based on the test for increasing trend in radiation dose.
[d] Based on 41,719 human subjects exposed to $1 rad (average = 29.5 rad).
† Lower confidence limit not reported by study authors.

factors), (2) epidemiological studies of populations that live in high and low background areas, and of populations of accidentally or occupational exposed persons, and (3) data from patients who have received diagnostic radiation and radiotherapy.

The use of human data pools theoretically provides the most direct and informative approach to assessing the toxicity of radiation in humans. This would likely be the case in laboratories using controlled exposure scenarios. Much of the information regarding exposures to radiation does not use a controlled exposure situation. Most of the human information comes from epidemiological studies following the detonation of nuclear bombs (Hiroshima, Nagasaki, Bikini Atoll, etc.), from accidents involving the release of radionuclides (Palomares, Spain; Thule, Greenland; Rocky Flats, Colorado; Hanford, Washington and others), or from exposed radiation workers or patients.

Epidemiology is the study of the incidence of disease in groups of people. Epidemiologists attempt to determine the risk factors that may cause health effects by comparing the rate of occurrence of a disease among exposed and non-exposed populations with similar attributes. Epidemiologists prefer to compare the rate of occurrence of the effects under consideration. The major questions asked are: (1) Do the rates of occurrence differ between populations? (2) Are any noted differences a real effect or are they merely due to chance? and (3) Is there a relationship between an agent or other risk factor (such as radiation) and

the effect? In studying populations, epidemiologists must characterize the subjects based upon both the risk factor and the disease status. There are three main types of observational epidemiological studies: cohort, case-control, and prevalence (cross-sectional). Prevalence studies measure the presence or absence of a disease in a particular population at a particular time. Cohort (or incidence) is a prospective study that looks at the development of a disease in an initially disease free cohort in the context of postulated risk factors. Case-control studies compare a population with an existing disease to a sex- and age-matched disease-free population.

Prevalence, cohort, and case-control studies are the most likely types of epidemiological studies to be conducted in the case of exposure to ionizing radiation. Cohort studies follow a group of initially healthy persons with differing levels of exposure or risk factors and compare the rate of occurrence of disease in each population over time. Because exposure is assessed prior to development of the effect, there is less chance for bias; in addition, the relationship of other disease outcomes to the pre-assessed risk factors may also be studied. In case-control studies, a population with a particular disease and a matched (except for the disease) disease-free population are assessed for exposure or risk factors in order to determine whether a causal relationship exists. By studying populations after the development of the disease, the causes of relatively rare diseases can be assessed without following thousands of people; thus, a case-control study is a quicker and less expensive study than a cohort study. However, there is more opportunity for bias due to the fact that the disease has already occurred prior to determining exposure or risk factors. Also, only one disease may be investigated per study.

All epidemiological studies have inherent weaknesses due to the potential for bias in the experimental design or implementation. Common forms of bias include selection bias, recall bias, misclassification, and confounding factors.

Selection bias occurs when subjects are not recruited uniformly. When information about health and exposure status is not collected consistently or reliably, this will also artificially affect the outcome of the study. Recall bias occurs when subjects do not uniformly report the incidence or severity of exposures or health effects. Misclassification refers to mislabeling or incorrectly characterizing a study participant with regard to the toxic end point or outcome (disease). A common type of misclassification occurs in patients with cancer; the cause of death in these subjects may be complicated and classified as the result

of a secondary illness. Even when death is attributed to cancer(s), the specific cancer listed on the death certificate may be a secondary metastatic cancer. Exposure may also be misclassified, particularly when study subjects are aware that they are practicing risky behavior. Confounding refers to the interaction of multiple factors on a given effect and the possibility of attributing risk to an inappropriate factor. For example, when assessing the risk of a disease due to a factor such as the wire code of high power lines (involving non-ionizing radiation), one must consider that the wire code of power lines may be highly correlated with urbanization, heavy traffic, and increased pollution, and not associated with the actual electric and magnetic field strengths to which individuals are exposed. In such a case, an association between power lines and disease must be investigated while taking these other factors into account; otherwise, the results and any statistical correlation found may not be interpretable or appropriate.

Epidemiological studies should be carefully crafted to identify and account for appropriate confounders, and their unique data interpreted objectively. The following pages contain a synopsis of some of the more important human radiation epidemiological studies.

#### 3.2.3.2 Nuclear Detonations of 1945 in Hiroshima and Nagasaki, Japan

The first atomic device was exploded in a test on July 16, 1945, in Alamogordo, New Mexico. The U.S. military, in an effort to bring a swifter end to the war and to avoid the casualties of a ground invasion of Japan (actually planned for November 1945), detonated a $^{235}U$ atomic bomb over the city of Hiroshima, Japan, on August 6, 1945. Three days later, another atomic bomb using $^{239}Pu$ was detonated over the city of Nagasaki, Japan. In both Hiroshima and Nagasaki, a total of 64,000 people within 1 km of the air detonation site (the air detonation side is designated as the "epicenter" and the point on the ground below the epicenter is designated as the "hypocenter" or "ground zero) were killed by a combination of the blast, intense heat, and to a much lesser extent gamma and neutron radiation emitted by these bombs. Blast, heat and light, and ionizing radiation accounted for 50%, 35%, and 15%, respectively, of the energy released by the bombs (Glasstone and Dolan 1977; Zajtchuk 1989). Survivors 1–2 kilometers away from the hypocenter received up to several hundreds of rad (several gray) of radiation and suffered the ill effects of ARS. The doses dropped off fairly rapidly with distance. In Hiroshima, the dose at 1 km was on the order of 100 rad (1 Gy), dropping to approximately 1 rad (0.01 Gy) at 2 km. For Nagasaki, the doses were on the order of 1,000 rad (10 Gy) and 10 rad (0.1 Gy), respectively. Those who survived the immediate effects, including those who were far enough away or shielded from a portion of the radiation,

were potential candidates for the latent effects of radiation. A more in-depth discussion of the events surrounding the creation of the atomic devices appears in Chapter 2 of this toxicological profile.

A few years after the atomic bombs were detonated, an effort was begun to study the effects that the different doses of ionizing radiation had on the surviving populations of Hiroshima and Nagasaki. This study was instituted by the Atomic Bomb Casualty Commission (ABCC) in 1950; the effects continue to be monitored today by the Radiation Effects Research Foundation (RERF). Periodic reports are published on the effects of ionizing radiation in the human populations of these cities in the main study, called the Lifespan Study (LSS). The LSS includes 120,321 individuals living in Hiroshima and Nagasaki in 1950; of these, 91,228 were exposed at the time of the bombing (BEIR V 1990).

At the time of the bombing of both cities, it was not possible to determine the exact doses of ionizing radiation each person had received; therefore, estimates were made as to the dose of radiation received by persons located at different distances from the hypocenter. The dose estimates, called the Tentative 1965 Dose (T65D), used the air dose (gamma ray + neutron kerma in air) adjusted for shielding by structures and natural terrain based on data obtained at the Nevada test sites, the Bare Reactor Experiment Nevada (BREN) experiment, and from large-scale shielding experiments. The accuracy of this computational system was questioned in 1978. After re-examining the available data, a new system of dose estimation, the Dosimetry System 1986 (DS86), was created and is available in its final format (Roesch 1987). The DS86 system provides more accurate radiation dose estimates than the T65D estimates because of improvements in assessing shielding of building materials, in verifying the gamma-ray component of the radiation doses to survivors using thermoluminescence of quartz crystals in roof tiles, and in considering the reduction in the neutron component of the radiation dose caused by the high humidity in Japan as compared to the Nevada desert. The DS86 data are currently being reevaluated, largely because of differing opinions on the magnitude of the Hiroshima neutron doses, which could produce small changes in the individual dose estimates, and because these doses directly affect the risk estimates

Based on the new dosimetry system, there are sufficient data from these large-scale human exposures to derive some conclusions about the cancer-inducing effects of external radiation. A report by Shimizu et al. (1988) used the exposure data from 75,991 survivors of the atomic bombs at Hiroshima and Nagasaki (based on the DS86 dosimetry) to estimate the risk of developing cancer when humans are exposed to radiation. Of these 75,991 exposed persons, 59,784 were distally exposed and 16,207 were proximally

exposed to the explosions. These persons are being followed to their time of death from 1950, with the specific types of cancers found through 1985 in these deceased individuals summarized in Table 3-9. The Radiation Effects Research Foundation (RERF) plans to continue studying the survivors and their offspring throughout the survivor lifespan in order to further refine the risk estimates.

As shown in Table 3-9, external radiation induces site-specific cancers in some organs but not in others. This extensive data set indicates that leukemia (acute and chronic myeloid and acute lymphocytic, but not chronic lymphocytic), cancers of the esophagus, stomach, colon, lung, female breast, ovary, and bladder, and multiple myelomas have statistically significant increases in incidences after exposure to radiation. The incidence of these types of cancer increases with the dose (as measured by estimated relative risk at 100 rad [1 Gy] and excess risk per 10,000 individuals each exposed to 100 rad [1 Gy] [$10^4$ person-year Gy]). Conversely, incidences of cancers of the rectum, gallbladder, pancreas, uterus, brain, and prostate, and incidences of malignant lymphoma do not appear to increase after exposure to ionizing radiation.

A number of other conclusions can be drawn from the data sets that are presented in many extensive tables in the Shimizu et al. (1988) report. Due to the size of these data sets, much of the raw data has been omitted from this toxicological profile.

Table 3-9 shows the risks associated with certain types of cancers over all age groups; when cancers are further classified by age at the time of death (ATD) and age at the time of the bombing (ATB), other trends are seen. For ATB <10 years, the risk of stomach cancer appears to be greater for those younger ATD groups (as observed for all cancers), but this trend is not statistically significant. No definable trends are observed for breast, lung, and colon cancers; this is most likely because in 1985, this age group had not yet reached the age where expression is likely. However, the relative risk of leukemia peaked at 6–8 years after the bombing and tends to decrease every year thereafter.

In humans, cancers do not begin to appear immediately after exposure to radiation; it is only after some minimum latent period (defined in this study as the time from exposure to the time of observation) that cancers induced by the effects of radiation will occur. This is the case with leukemia and with solid

tumors shown in Table 3-9. The incidence of radiation-induced leukemia began to occur 2–3 years after the detonation occurred, reached a peak within 6–8 years, and has been steadily declining ever since. A small (yet significant) excess in leukemia mortality still existed as of the writing of the Shimizu et al. (1988) report. This study also suggested that the incidence rate of radiation-induced cancers increases significantly only when the survivors reach those ages at which cancers normally develop. Thus, the minimum latent period is longer for the younger irradiated groups. These data also have demonstrated that the latent period for all the cancers shown in Table 3-9 (except for leukemia) appears not to be dose-dependent; the latency period is not affected by the dose. The latency period, however, is shorter among the young who were exposed to higher doses within the first 10 years of life. For the solid tumors (all but leukemia), the data from this study suggest that the minimum latent period is 15–19 years for stomach cancer, 20–24 years for lung and breast cancers, 25–29 years for ovarian cancer, and 30–34 years for cancers of the colon and urinary tract and for multiple myeloma. Some benefits of following this group until the last individual dies are (1) the improvement of radiogenic cancer risk estimates and (2) the possibility of verifying that certain cancer types whose incidence rates have not increased may have very long latency periods.

Other factors were examined in this cohort that may affect cancer rates. The relative risk of developing leukemia was not significantly different for males and females. For cancers other than leukemia, particularly those of the esophagus and lung, the relative risk is higher for females than for males. As for the effect of smoking on the rate of development of lung cancers, the relative risk of lung cancer at 100 rad (1 Gy) is greater for females than males. Adjusting for the effects of smoking in both males and females, the relative risk differences no longer are statistically significant. Also, no shortening of the lung cancer latency period was noted in male or female smokers.

The Shimizu et al. (1988) report addressed the occurrence of leukemia in the populations of Nagasaki and Hiroshima; the report did not elaborate on the specific types of leukemia found in those populations as a result of age and dose. Tomonaga et al. (1993) reported on the differential effects of radiation in inducing major leukemia types in these two cities using the DS86 dosimetry system. That study included 766 leukemia cases (249 among LSS subjects) occurring as of the end of 1980 in people who were exposed within a 9-kilometer radius of the detonation hypocenter. Bone marrow and blood specimens of

the registered cases were reassembled and re-examined for 493 of the 766 leukemia-diagnosed cases, including 177 of the 249 LSS cases, using the French-American-British classification system of leukemia diagnosis. Leukemias were further subclassified into a specific type of leukemia: acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and other leukemias (OTHER, including adult T-cell leukemia and other specifically diagnosed leukemias). Once a diagnosis was ascertained, the type of leukemia was correlated with the total body kerma received by that person, the city the dose was received in, and the elapsed time since exposure. Incidence estimates for each type of leukemia by exposure category and time period were determined (see Table 3-8) as well as incidence estimates for each type of leukemia by exposure category (see Table 3-9).

Meaningful statistical analysis on the leukemia data set could not be performed and should be taken as descriptive only. For the three lowest exposure categories, incidence rates were either similar or slightly increased over time; the two highest dose categories had incidence rates for all types of leukemias declining over time. CML and OTHER leukemia incidence rates returned to background levels during the late 1970s, while at the highest exposure levels ($150 rad [1.5 Gy]), the overall incidence rates of ALL and AML were 4–5 times higher than background levels from 1976 to 1980. The age at time of bombing seemed not to modify the temporal trends of leukemia in the three lowest exposure groups. Tomonaga et al. (1993) states in regard to this data, "In the two highest exposure groups, type-specific incidence rates declined with time in the youngest age-ATB group (0–15 years) for all types. In the young adult age-ATB group (16–35 years), however, this pattern held for ALL and CML in the two highest exposure categories and for OTHER in the 50–149.9 rad (0.5–1.499 Gy) group. The incidences of OTHER among those exposed to $1.5 Gy (150 rad) and of AML among those exposed to 50–149.9 rad (0.5–1.499 Gy) held nearly constant in time and that of AML among those exposed to >150 rad (1.5 Gy) increased. Among older adults (i.e., $36 years old ATB), there was either no change or an increase in incidence over time for AML and OTHER in the two highest exposure categories. CML and OTHER rates declined with time in the 50–149.9 rad (0.5–1.499 Gy) group, and CML and CML and ALL declined with time in the $150 rad (1.5 Gy) group. There was an increase over time in the excess rates of AML among those exposed to very high radiation levels ($150 rad [1.5 Gy]) at adult ages ATB. Thus age ATB appears to moderate the temporal patterns of incidence in the highest exposure groups." The incidence estimates for these types of leukemias suggest that the incidences for ALL, AML, CML, and OTHER were all greater in the higher dose categories. In the highest dose group, the estimated incidence

of ALL decreased with increasing age ATB, while those of ALL, CML, and OTHER were less dependent on age ATB. The risks of ALL and CML increased more rapidly with an increasing dose than did those of AML and OTHER. These findings suggest that ALL and CML leukemogeneses are more affected by atomic bomb radiation production than AML.

#### 3.2.3.3 Human Exposures to $^{226}$Ra and $^{228}$Ra: The Radium Dial Painters

Radium was one of the first radioactive isotopes discovered (see Chapter 2). It was used in medicines and concoctions around 1900; however, the highest exposures to radium involved its use in dial paint. Martland (1931) reported that approximately 800 females employed in a factory in New Jersey painted the dials of watches and clocks with special luminous paint. The paint consisted of a crystalline, phosphorescent zinc sulfide, with the addition of varying amounts of radium and its progeny containing primarily $^{226}$Ra, $^{228}$Ra, and $^{228}$Th, all in the form of insoluble sulfates in the paint. These young women "tipped" or pointed the end of the paint brush with their mouth and lips whenever needed to restore a sharp painting point. This resulted in oral ingestion of small amounts of radium, mainly $^{226}$Ra ($t_{1/2}$ = ~1,600 years) and $^{228}$Ra ($t_{1/2}$ = 5.75 years). In the women who died, deposits of these isotopes were found over the entire skeleton, and in particular in the cortical bone surface. Martland also estimated the total lifetime body burden of radium to be between 2 and 20 µg Ra in those exhibiting clinical signs of "radium poisoning." Radiation toxicity seemed more evident in those individuals who worked at the factory for >1–2 years or who had swallowed the paint for >1–4 years.

One of the main findings in this study was the increased incidence of death in some of the exposed women. Death was noted in 18 women in the study. Thirteen of the women who died also had jaw necrosis and anemias that developed within 4–6 years after they left the factory for other employment. The other eight deaths occurred at a later date. Jaw necrosis and anemia occurred with less severity and at lower levels; these individuals developed bone lesions which were characterized as radiation osteitis. Osteogenic sarcomas (scapula, knee, pelvis, femur, orbit) also developed in this study population.

A study by Evans et al. (1966) at the Massachusetts Institute of Technology (MIT) reported on the incidence of tumors in individuals exposed to $^{226}$Ra and $^{228}$Ra in both the radium dial painter population and other populations exposed to alpha emitters. The study included approximately 5,000 or more persons, including chemists who inhaled or ingested radioactive compounds, patients receiving

intravenous injections of $^{224}$RaCl, those who ingested water containing $^{224}$Ra, and the female radium dial painters. As a group, the total duration of exposure was usually less than 1 year but in some cases was as long as 20 years. The conclusion from this study confirmed the study findings of both Martland (1931) and Rowland et al. (1978)— people who inhale or ingest radium ($^{224}$Ra, $^{226}$Ra, $^{228}$Ra) have an increased chance of developing tumors of the bone or of the paranasal sinuses but little, if any, chance of developing leukemia from any of the doses studied. The data also supported the conclusion that the time required to develop these sarcomas or carcinomas tended to increase as the total activity of radium decreased. When all measured cases were included, the skeletal dose at which tumors began to be observed was 1,200 rad (12 Gy) of alpha radiation. No tumors were observed in the population that received less than 1,200 rad (12 Gy), the "practical threshold"; the tumor incidences began to climb in a linear dose-response manner from 1,200 to 50,000 rad (12–500 Gy) skeletal dose. Not all persons receiving a >1,200 rad (12 Gy) skeletal dose developed sarcomas or carcinomas; the tumor incidence at >1,200 rad (12 Gy) skeletal dose was placed at 40% at the time the study ended. Rowland et al. (1978) conducted a follow-up study on the incidences of osteosarcoma and "head carcinomas" (carcinomas originating in the mastoid air cells or paranasal sinuses) on this population of female dial painters. The data sets are shown in Tables 3-10 and 3-11.

Using statistics from the U.S. Department of Labor (DOL), it was estimated that approximately 2,000 individuals had been employed in the radium dial painting industry prior to 1929, with 1,474 workers identified who worked in the industry prior to 1930. Most of the dial workers were not located until as late as the 1960s. For the osteosarcoma analysis, the combined intake of radium ($^{226}$Ra + $^{228}$ Ra) ranged from <0.5 to $2,500 µCi (0.02–92 MBq), with the time-weighted average ranging from 0.74 to 3,602 µCi (0.03–133 MBq). The average age at first exposure to these two isotopes ranged from 18.4 to 19.8 years. For the head carcinomas, the intake of $^{226}$ Ra ranged from <0.5 to $1,000 µCi, with the time-weighted average ranging from 0.71 to 1,577 µCi. The average age at first exposure ranged from 17.8 to 22.3 years. The increased incidence of osteosarcoma in this exposed population can be attributed in part to radium's distribution and elimination kinetics. Radium has distribution patterns similar to those of calcium. Once ingested, radium distributes primarily to the bone surfaces and within about 10 µm from the osteogenic cells (the target cells for radium toxicity). The range of alpha particles in soft tissue is estimated to be approximately 30–70 µm (see Chapter 2), well within the range of these radiosensitive

**Table 3-10. Distribution of Osteosarcomas in a Population of Female Dial Painters Exposed to $^{226}$Ra and $^{228}$Ra**

| Systemic intake[a] ($^{226}$Ra + 2.5 $^{228}$Ra)[b] | | | | | | | |
|---|---|---|---|---|---|---|---|
| Activity range (μCi) | Activity weighted average (μCi) | Number of cases | Average age at first exposure (years) | Number of bone sarcomas | Person-years | Person-years at risk | Sarcomas per 1,000 person-years at risk ($10^{-3}$ years $^{-1}$) |
| $2500 | 3602 | 16 | 18.5 | 4 | 299 | 219 | 18.3 |
| 1000–2499 | 1675 | 22 | 19.2 | 15 | 529 | 419 | 36.8 |
| 500–999 | 675 | 18 | 19.7 | 8 | 700 | 610 | 13.1 |
| 250–499 | 375 | 32 | 19.8 | 9 | 1409 | 1249 | 7.21 |
| 100–249 | 171 | 27 | 18.4 | 2 | 1299 | 1164 | 1.72 |
| 50–99 | 68.0 | 21 | 18.6 | 0 | 1082 | 977 | 0.00 |
| 25–49.9 | 35.2 | 45 | 19.5 | 0 | 2331 | 2106 | 0.00 |
| 10–24.9 | 16.3 | 71 | 19.2 | 0 | 3642 | 3287 | 0.00 |
| 5–9.9 | 7.04 | 66 | 19.1 | 0 | 3378 | 3048 | 0.00 |
| 2.5–4.9 | 3.63 | 83 | 18.8 | 0 | 4217 | 3802 | 0.00 |
| 1.0–2.49 | 1.56 | 101 | 18.9 | 0 | 5240 | 4735 | 0.00 |
| 0.5–0.99 | 0.74 | 52 | 18.4 | 0 | 2731 | 2471 | 0.00 |
| <0.5 | --- | 205 | 19.0 | 0 | 10535 | 9510 | 0.00 |

[a]estimated amount that entered the blood after oral exposure

[b]dose adjustment factor for $^{226}$Ra (and daughters) energy (29.4 MeV) and $t_{1/2}$ (1600 years), in relation to $^{228}$Ra (and daughters) energy (10.6 MeV) and $t_{1/2}$ (5.75 years)

Source: Rowland et al. 1978

cells but outside the range of red marrow cells from which leukemias would originate. The osteogenic cells initially receive a large radiation dose after each intake of $^{226}$Ra and/or $^{228}$Ra. Owing to the long physical $t_{1/2}$ of both $^{226}$Ra ( - 1,600 years) and $^{228}$Ra (5.75 years), both radionuclides will eventually redistribute throughout the bone matrix over time, moving out of range of the osteogenic cells but continuing to irradiate other less sensitive cells and tissues within a 70-μm radius of each atom of radium. A similar proximity of exposure scenario is likely true for the development of the head carcinomas in this population of exposed workers. The most likely explanation for the head carcinomas is that they are due to accumulation of $^{222}$Rn gas and radon daughters in the mastoid air spaces of the sinus cavities. This explains the lack of effect of $^{224}$Ra and $^{228}$Ra, which transform through $^{220}$Rn by short half-life transitions, and which produce much lower doses in the parasinal cavities than from $^{222}$Rn (Rowland 1994).

**Table 3-11. Distribution of Head Carcinomas in a Population of Female Dial Painters Exposed to $^{226}Ra$**

| Systemic intake[a] ($^{226}Ra$) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Activity range (μCi) | Activity weighted average (μCi) | Number of cases | Average age at first exposure (years) | Number of head carcinomas | Person-years | Person-years at risk | Carcinomas per 1,000 person-years at risk ($10^{-3}$ years $^{-1}$) |
| $1000 | 1577 | 10 | 17.8 | 3 | 264 | 164 | 18.3 |
| 500–999 | 584 | 11 | 22.3 | 2 | 385 | 275 | 7.27 |
| 250–499 | 366 | 25 | 20.1 | 5 | 1062 | 812 | 6.16 |
| 100–249 | 176 | 31 | 18.3 | 5 | 1255 | 945 | 5.29 |
| 50–99 | 68.3 | 23 | 18.2 | 1 | 1123 | 893 | 1.12 |
| 25–49 | 35.5 | 34 | 18.8 | 1 | 1666 | 1326 | 0.75 |
| 10–24.9 | 15.9 | 59 | 19 | 0 | 3025 | 2435 | 0 |
| 5–9.9 | 6.99 | 41 | 18.4 | 0 | 2114 | 1704 | 0 |
| 2.5–4.9 | 3.52 | 70 | 19.6 | 0 | 3558 | 2858 | 0 |
| 1.0–2.49 | 1.55 | 145 | 19.3 | 0 | 7531 | 6081 | 0 |
| 0.5–0.99 | 0.71 | 73 | 18.7 | 0 | 3799 | 3069 | 0 |
| <0.5 | – | 227 | 18.9 | 0 | 11624 | 9354 | 0 |

[a] estimated amount that entered the blood after ingestion

Source: Rowland et al. 1978

The data presented in both tables show that a dose response is present when comparing the weighted-average dose to the number of osteosarcomas or head carcinomas observed throughout the lifespan of these exposed individuals. In addition, a dose-squared-exponential function most closely described the bone sarcomas induced by these two radionuclides. In contrast, a linear dose-response function was found to best describe the head carcinoma data.

### 3.2.3.4 Human Exposures to $^{224}Ra$ via Injection

During 1944–1951, injections of $^{224}Ra$ were administered to approximately 2,000 German adults and children as a treatment modality for several debilitating diseases, including tuberculosis and ankylosing spondylitis. A report by Spiess and Mays (1970) summarized the health effects of 925 humans (708 adults and 217 children) injected with $^{224}Ra$ who received alpha doses of up to 5,750 rad (57.7 Gy). The duration of treatment ranged from a few weeks to a few years, depending on the disease being treated.

For this study, treated individuals were classified by age and dose received during the treatment period(s). These subpopulations are shown in Tables 3-12 and 3-13.

As was the case with $^{226}$Ra and $^{228}$Ra, the critical organ for $^{224}$Ra was bone tissue, with an overall increased incidence of osteosarcoma in the exposed population. Tables 3-12 and 3-13 report the dose parameters and incidences of osteosarcomas induced by $^{224}$Ra by age distribution. These data show that the lowest dose that resulted in a detectable osteosarcoma was 90 rad (in an adult). The incidence of osteosarcoma in this population increased in a dose-responsive fashion, with a 0.7% rise in incidence of osteosarcomas per 100 rad (1 Gy) skeletal dose from $^{224}$Ra in adults and a rise of 1.4% per 100 rad (1 Gy) in children (see Table 3-13). The ability of $^{224}$Ra to induce bone tumors in males and females, with or without pre-existing bone disease, was equal in all instances. At the time of publication of the Speiss and Mays (1970) report, no head carcinomas or leukemias attributable to $^{224}$Ra exposure had been observed.

The lowest alpha dose to induce osteosarcoma in this population exposed to $^{224}$Ra was 90 rad (0.9 Gy), significantly lower than the 1,200 rad (12 Gy) (skeletal dose at death) required to induce osteosarcoma in the radium dial painters ($^{226}$Ra and $^{228}$Ra). The answer lies in the physical half-life of $^{224}$Ra, and the total dose to the critical tissue. $^{224}$Ra distributes in an identical fashion within the bone matrix as does $^{226}$Ra and $^{228}$Ra, with the initial deposition of each of these isotopes within 10 μm from the osteogenic cells on the bone surface. In cases of $^{226}$Ra and $^{228}$Ra exposure, the dose of radiation was initially received by the osteogenic cells; however, as time progressed, natural bone formation (remodeling) resulted in the redeposition of these isotopes (and other minerals) away from these target cells and into the mineral volume of the bone, out of the range of the alpha particles (50–70 μm) emitted by these isotopes. These longer-lived isotopes continued to transform for several years; however, many of the radium atoms were out of range of the target tissues (osteogenic cells) and not likely to cause bone cancer. This was not the case with those exposed to $^{224}$Ra. $^{224}$Ra deposits initially on bone surfaces as does $^{226}$Ra and $^{228}$Ra; however, the half-life of $^{224}$Ra is 3.62 days and the dosimetery is quite different from other radium isotopes. The local dose to the skeleton of $^{224}$Ra within 0–10 μm is estimated to be nine times the average skeletal dose of $^{226}$Ra (because the radiation dose is almost exclusively delivered to the osteogenic cells during $^{224}$Ra's short half-life). However, the dose from $^{226}$Ra to the critical osteogenic cells is only 0.63 times the average skeletal dose, which is randomly distributed throughout the bone matrix.

## Table 3-12. Alpha Doses from Injected $^{224}$Ra (in rad) by Age Group, Number, and Percentage of Subpopulation Developing Osteosarcoma

| | | Age at first injection of $^{224}$Ra | | | | | |
|---|---|---|---|---|---|---|---|
| Dose range (rad) | Parameters | 1–5 years | 6–10 years | 11–15 years | 16–20 years | All children (1–20 years) | Adults (>20 years) |
| 0–89 | Average rad dose | 46 | ND | 24 | 55 | 47 | 53 |
| | No. of persons | 1 | ND | 1 | 3 | 5 | 210 |
| | % Bone sarcomas[a] | 0.00 | ND | 0.00 | 0.00 | 0.00 | 0.00 |
| 90–199 | Average rad dose | 152 | 126 | ND | 148 | 146 | 139 |
| | No. of persons | 2 | 1 | ND | 4 | 7 | 229 |
| | % Bone sarcomas | 0.00 | 0.00 | ND | 0.00 | 0.00 | 1.3 |
| 200–499 | Average rad dose | 446 | 397 | 344 | 342 | 363 | 306 |
| | No. of persons | 2 | 9 | 7 | 17 | 35 | 214 |
| | % Bone sarcomas | 0.00 | 0.00 | 29 | 0.00 | 5.7 | 1.9 |
| 500–999 | Average rad dose | 860 | 703 | 727 | 719 | 727 | 650 |
| | No. of persons | 7 | 30 | 22 | 17 | 76 | 55 |
| | % Bone sarcomas | 0.00 | 10 | 5 | 0.00 | 5.3 | 5.5 |
| 1000–1999 | Average rad dose | 1426 | 1381 | 1340 | 1246 | 1345 | ND |
| | No. of persons | 16 | 19 | 18 | 19 | 72 | ND |
| | % Bone sarcomas | 38 | 26 | 22 | 21 | 26.4 | ND |
| 2000–5750 | Average rad dose | 3491 | 3451 | 2550 | 3100 | 3329 | ND |
| | No. of persons | 9 | 9 | 3 | 1 | 22 | ND |
| | % Bone sarcomas | 22 | 67 | 0.00 | 0.00 | 36.4 | ND |
| All persons with a known dose of $^{224}$Ra | Average rad dose | 1662 | 1207 | 984 | 747 | 1103 | 204 |
| | No. of persons | 37 | 68 | 51 | 61 | 217 | 708 |
| | % Bone sarcomas | 22 | 21 | 14 | 7 | 15.2 | 1.4 |

[a] % of bone sarcomas as of 1969 ND = No data available

Source: adapted from Speiss and Mays 1970

**Table 3-13. Age Distribution, Alpha Dose (in rad), and % Incidence of Osteosarcomas Induced by $^{224}$Ra Injection**

| Age (years) | Exposed patients | Sarcoma cases | % Incidence | Average dose (rad) | % Incidence per 100 rad |
|---|---|---|---|---|---|
| 1–5 | 37 | 8 | 21.6 | 1662 | 1.30 |
| 6–10 | 68 | 14 | 20.6 | 1207 | 1.70 |
| 11–15 | 51 | 7 | 13.7 | 984 | 1.39 |
| 16–20 | 61 | 4 | 6.6 | 747 | 0.88 |
| All children | 217 | 33 | 15.2 | 1103 | 1.38 |
| Adults | 708 | 10 | 1.4 | 204 | 0.69 |

Source: adapted from Speiss and Mays 1970

Other similar studies include those involving tinea capitis treatment (Albert et al. 1986; Harley et al. 1983; Ron and Modan 1984), uranium miners (NIH 1994), and iron miners (Radford and Renard 1984).

### 3.2.3.5 Other Human Cancer Studies

Cancer data from other sources are available in the open literature. Sorahan and Roberts (1993) performed a case-control study examining the association between childhood cancer and the occupational exposure of the child's father to radiation. Data from the Oxford Survey of Childhood Cancers collected from 1953 to 1981 were used. There was a total of 15,279 cases and the same number of matched controls (matched for sex, date of birth, and local area). Estimates of exposure were completed based on job descriptions. Dose groups were: not exposed (<0.1 rem, 0.001 Sv), 0.1–0.4 rem (0.001–0.004 Sv), 0.5–0.9 rem (0.005–0.009 Sv), and $1 rem (0.01 Sv). There were also 27 case fathers and 10 control fathers who had been exposed to radionuclides. Based on the information gathered, it was determined that 67 fathers of children with cancer and 50 fathers of controls were exposed to external radiation within 6 months of conception of their children. Relative risks for estimated external radiation doses and all childhood cancers were near one, and none of the specific types was statistically significant. Among fathers with likely exposure to radionuclides (from unsealed radioactive material), the relative risk for all childhood cancers was statistically significant at 2.87 (95% CI 1.15–7.13). There is considerable uncertainty associated with this value, and the findings are not supported by those in the studies of the survivors of the atomic bombings in Japan. Cancer incidence during the first 20 years of life among the children of parents who suffered a mean gonadal dose of 43 rem (0.43 Sv) was 43 cases in 31,150 offspring, and there were 49 cases among 41,066 offspring from the control population. For leukemia,

there were 16 cases among 31,150 children of exposed parents and 21 cases among the 41,066 children from the unexposed controls (Yashimoto et al. 1991).

In 1991, Matanoski (1991) reported on the health effects of low-level radiation exposure to shipyard workers. Many of the earlier human radiation studies had been of groups exposed to large doses of radiation where there was a clear dose response for cancer induction. The typical dose response curve assumes a linear no-threshold shape that starts with zero effect at zero dose and extends linearly upward to intersect the measured effect at doses above 10–40 rad (0.1–0.4 Gy). Previous attempts to demonstrate the shape of the curve at low and occupational doses had not produced a clear result. The purpose of the Matinoski study was to better define the upper and lower bounds of risk associated with radiation exposure using a relatively large population group whose radiation doses had been measured carefully, many of which were elevated above ambient levels, and for which there was an adequate control population. The selected group was workers in public and private U.S. shipyards involved in the overhaul and refueling of nuclear-powered warships. Concern over the risk to these workers had been raised earlier in a limited study of deaths among Portsmouth, New Hampshire, shipyard workers (Najarian 1978). Also, a report had been released on an apparent leukemia excess among U.S. military veterans (Caldwell 1980). However, a subsequent cohort study by Rinsky (1981) did not observe a relationship between exposures and leukemia. These groups had received approximately the same radiation dose. The Matinoski study group involved workers at eight nuclear facilities throughout the United States, who had been occupationally exposed from 1957 through 1981. The study group was divided into dose groups and exposures were lagged by 2 years for leukemia and lymphoma, and 5 years for lung cancer to account for disease latency. The numbers in each of the three major dose groups were: 32,510 non-radiation workers, 10,348 radiation workers whose doses were below 0.5 rem (0.005 Sv), and 27,872 radiation workers whose doses were over 0.5 rem (0.005 Sv). The data were analyzed statistically using methods suggested by Gilbert (1983). In this manner it was estimated that the statistical power had a 79% probability of finding a risk of leukemia from cancer if the risks were as large as five times the linear model estimates in BEIR III (1980). For those whose doses exceeded 0.5 rem (0.005 Sv), the death rate from leukemia was only 91% of the normally expected death rates from that disease (95% confidence interval = 56–139%), and the death rate from lymphatic and hemopoietic cancers was 82% (95% confidence interval = 61–108%) of the normally expected death rates from those diseases. The death rates from these diseases in the less than 0.5 rem (0.005 Sv) group were similar to those in the above 0.5 rem (0.005 Sv) group. Standard mortality ratios (SMRs) for the lower-dose group were similar. This

indicates the risks of these diseases is lower among shipyard workers than in the general population. The risk of lung cancer, however, was significantly higher ($p<0.05$) in the non-nuclear work group and slightly higher in the nuclear work groups than for the public. Mesothelioma was selected as a biological marker for the presence of asbestos exposure in the population, and a high SMR for mesothelioma (>5 for radiation workers and 2.4 for non-radiation workers) suggests that the excess is due to asbestos exposure and not to radiation. The radiation worker population did not show a significant increase in the risk of any of the cancers studied, except for mesothelioma which was attributed to asbestos. The data suggest that there is a threshold greater than 0.5 rem (0.005 Sv) for leukemia, and lymphatic and hemopoietic cancers.

In another human study, Checkoway et al. (1988) used a historical cohort mortality study of 8,375 workers at the Y-12 plant at Oak Ridge who were exposed to gamma radiation and/or alpha radiation by inhaling uranium compounds. The population studied included employees who had worked for at least 30 days between May 1947 and December 1974. The median duration of exposure in that study was 9.2 years. There were 862 deaths in the cohort, which was composed of 6,781 white males. The majority of the cohort was followed for 10 years. Exposure from gamma radiation was measured with dosimeters or film badges, and internal alpha contamination was estimated with urinalysis for uranium (reported as cumulative radiation dose). Mortality was compared with both U.S. and Tennessee rates. For all causes there were fewer deaths than expected (Standardized Mortality Ratio [SMR] 0.89, 95% CI 0.84–0.96). These findings are consistent with the healthy worker effect. There were a total of 196 cancer deaths in the population compared to 193 expected, (SMR 1.01). Relative to U.S. white males, there were statistically significant excesses of lung cancer (SMR 1.36, 95% CI 1.09–1.67) and possibly cancers of the and central nervous system (SMR 1.8, 95% CI 0.98–3.02). Cancer SMRs for Tennessee white males were lower than those for the U.S. white male referent population. A trend was observed for increasing lung cancer deaths with increasing radiation dose, although the trend was greater with a zero-year latency assumption than for a 10-year latency assumption. Mortality for brain and central nervous system cancers was unrelated to either the alpha or gamma dose. The authors point out that the dose-response trend for lung cancer mortality should be viewed with some caution because the rate ratio estimates are imprecise, as reflected by the wide confidence limits because of small numbers. Also, the dose-response gradients are reduced considerably when a 10-year latency is assumed. No data on cigarette smoking were included in the study. Other studies have also shown that the lung is the primary target organ of airborne radon when mixed with diesel fumes, cigarette smoke and silica dust related to uranium mining, but not from uranium itself (BEIR IV 1988), which was the most important airborne radioactive material at this

plant. Readers are referred to the effects of cancer induced by the chemical and radiological effects of uranium mining in the ATSDR *Toxicologic Profile for Uranium* (ATSDR 1999b).

In a later related report, Kneale et al. (1981) responded to criticism of previous reports of a study of cancer risks from radiation to workers at Hanford using the method of regression models in life-tables. The population included employees up to 1975 who wore film badges for their external dosimetry record and included deaths through 1977. Some internal monitoring was also completed: individuals for whom internal monitoring was completed tended to have higher external exposures. Cause of deaths was classified into three categories: (1) cancers of radiosensitive tissues (stomach, large intestine, pancreas, other intestinal, pharynx, lung, breast, lymphoma, myeloma, myeloid leukemia, other reticuloendothelial system cancers, and thyroid); (2) other cancers; and (3) non-cancer. The reported risk per unit of radiation dose for cancers of radiosensitive tissues was much greater than the generally accepted risk based on other studies which had been used in setting safety levels for exposure to low-level ionizing radiation. The estimated risk calculated from this study was about 10–20 times greater than would have been expected by extrapolating downward from higher doses analyzed in previous studies, notably studies of the atomic bomb survivors. The authors suggested that after statistically controlling for a wide range of possible interfering factors, there was a significant downward curve at about 10 rem (0.1 Sv) in the dose-response relationship. Therefore, the agreement with other studies, conducted at higher doses, may be stronger than is widely assumed. The authors also point out that the findings on cancer latency (about 25 years) and the effect of exposure age (increasing risk with age) are in general agreement with other studies. The unexplained finding is a significantly higher dose for all workers than for workers who developed cancers in tissues that are supposed to have low sensitivity to cancer induction by radiation. The “healthy worker effect” was very large in this study—the SMR for all causes of death was 75. Therefore, the fact that living workers at Hanford in Washington State have higher radiation doses than workers who died could reflect a healthy worker effect. Using a model that allowed for cancer latency and variation in sensitivity to radiation with age of exposure, investigators estimated a doubling dose for cancer of 15 rad (0.15 Gy) with a 95% CI of 2–150 rad. The interval between cancer induction and death was estimated (maximum likelihood estimate) to be 25 years. The investigators also discuss the fact that Japanese bomb survivor data and ankylosing spondylitis data indicate that the doubling dose is about 200 rem (2 Sv). No records of smoking were available for the Hanford population. Internal monitoring showed evidence of internal exposure in only 225 of the Hanford workers; the investigators indicate that

the effects were a result of external rather than internal radiation. The authors pointed out that the Hanford study could not distinguish between effects of neutron and gamma radiation.

#### 3.2.3.6 Laboratory Animal Reports

Cancer is a major latent biological effect of inhaling many of the various isotopes and chemical forms of radioactive materials. The literature contains many studies describing the onset and specific types of cancers that occur after inhalation exposure(s) (see the ATSDR profiles on uranium and radon for more complete information). The vast majority of reports concerning the inhalation of radionuclides with the subsequent development of cancer dealt with alpha and beta particle emitters incorporated into soluble or insoluble particles of varying sizes for an acute duration of delivery (usually only a few minutes to achieve the desired initial lung burdens) followed by a long-term exposure of the tissues. Due to the large database describing the neoplasia associated with exposure to ionizing radiation, only a cross-section of these reports will be discussed in some detail here.

Cancer has been reported in laboratory animals after inhalation of different radionuclides (see Table 3-1). For example, isotopes of strontium ($^{85}Sr$ and $^{90}Sr$) have strong affinities for bone; therefore, it is reasonable to expect that the initial site of neoplasia formation will be in bone tissues. Metastases may occur to more distant organs at a later time, depending on the type of tumor induced. For example, Gillett et al. (1987b) studied the late-occurring biologic effects in Beagle dogs given graded levels of $^{90}SrCl_2$ via single brief inhalation exposures and then observed for their lifespans. The cumulative absorbed beta dose to bone ranged from 12 to 1,200 rad (0.012–12 Gy) at 30 days and from 200 to 170,000 rad (92–1,700 Gy) at 1,000 days after exposure. The most frequent cause of death in exposed dogs was primary bone cancer (30 of the 66 exposed dogs). Bone-tumor-related deaths occurred from 759 to 3,472 days after exposure. Four additional animals developed carcinomas in soft tissues adjacent to the bones of the skull (invasive baso-squamous carcinoma, transitional carcinomas of the nasal cavity, and an adenocarcinoma in the maxilloturbinate region). The remaining exposed and control dogs died from a variety of other causes not related to $^{90}Sr$ exposure. Radiation-induced lesions were confined to the bone, bone marrow, and adjacent soft tissue. Forty-five primary bone tumors occurred in 31 of the 66 exposed dogs (47%). Metastasis occurred from 21 tumors, with the lungs being the most frequent site of metastasis (76%). Twenty-seven tumors were classified as different subtypes of osteosarcoma, 14 as hemangiosarcomas, 3 as fibrosarcomas, and 1 as a myxosarcoma.

Using $^{241}$Am, Gillette et al. (1985) determined the retention, translocation, and excretion of inhaled monodisperse (1.8 μm AMAD) or polydisperse aerosols (AMAD 0.75, 1.5, 3.0 μm) and explored the development of osteosarcomas in dogs. $^{241}$Am was soluble and transported in blood and deposited in the liver and skeleton. Two years after exposure, 0.5–3.0% of the initial lung burden was present in the lung, 10–47% was in the liver, and 10–36% in the skeleton. Four of 15 dogs developed osteoblastic osteosarcomas #1,000 days after exposure to $^{241}$Am. Three of these were in the 1.8-μm AMAD group and one was in the 3.0-μm AMAD group. Initial lung burdens for all 15 ranged from 1.0 to 6.2 μCi (0.04–0.2 MBq). Radiation doses to 1,000 days for dogs ranged from 185 to 1,260 rad (1.85–12.6 Gy) to the lungs, 180 to 1,070 rad (1.8–10.7 Gy) to the liver, and 67 to 410 rad (0.67–41 Gy) to the skeleton, while the skeletal doses to death for the 4 dogs developing osteosarcoma were 500, 300, 240, and 180 rad (5, 3, 2.4, and 1.8 Gy). Metastasis was evident in only 1 of the 4 dogs.

Neoplastic formation after exposure to $^{238}$Pu and $^{239}$Pu has been extensively studied in Beagles. Hahn et al. (1981) exposed 72 Beagle dogs by inhalation to monodisperse aerosols of $^{238}PuO_2$ measuring 1.5 μm and another 72 dogs to particles measuring 3.0 μm. Twenty-four control dogs inhaled an aerosol produced from a diluent solution. Equal numbers of males and females were used. Groups of 12 dogs were exposed to concentrations expected to produce initial lung burdens of 0.56, 0.28, 0.14, 0.07, 0.029, 0.01, and 0 μCi/kg (0.021, 0.010, 0.0052, 0.0826, 0.0011, 0.00037, and 0 MBq/kg). However, mean actual initial lung burdens were 0.97, 0.43, 0.26, 0.11, 0.055, 0.017, and 0 μCi/kg (0.0359, 0.0159, 0.0096, 0.0041, 0.0020, and 0 MBq/kg), respectively, for 1.5 μm particles, and 1.2, 0.57, 0.30, 0.14, 0.069, 0.024, or 0 μCi/kg (0.044, 0.021, 0.011, 0.0052, 0.0026, 0.00089, or 0 MBq/kg), respectively, for 3.0 μm particles. Necropsy and histopathological examinations were performed at death. Primary bone cancers developed in Beagle dogs briefly exposed by inhalation to aerosols of $^{238}PuO_2$. $^{238}PuO_2$ was initially deposited in the respiratory tract where it was retained with a half-time greater than 100 days. A portion of the $^{238}$Pu was solubilized and translocated to the liver and skeleton; 46 of 144 exposed dogs and 2 of 24 control dogs died (as of date of publication). Deaths unrelated to bone tumors are as follows: 7 of the 144 dogs died from severe radiation pneumonitis and pulmonary fibrosis 536–1,213 days after exposure (3,700–8,600 rad [37–86 Gy] to lungs) and 4 of the 144 dogs died of pulmonary carcinomas 1,319–2,143 days after exposure (2,100–5,900 rad [21–59 Gy] to lungs). Five years after exposure, 46 osteosarcomas developed in 35 of 144 exposed dogs. The cumulative absorbed radiation doses to the skeleton for these dogs ranged from 210 to 830 rad (21-83 Gy), and time from inhalation exposure to death ranged from 1,125 to 2,078 days. Of the 46 bone tumors, 22 originated in the vertebrae (49%),

12 in the humeri (26%), 6 in the pelvis (13%), and 6 in miscellaneous long and flat bones (13%). Most of the tumors were well differentiated sarcomas. Only 10 of the tumors metastasized; the lung was the organ most often invaded. Bone tumors were associated with lesions of radiation osteodysplasia. The number of bone tumors found in this study indicated that inhaled $^{238}PuO_2$ was an effective skeletal carcinogen. The authors noted that the rate of solubilization in the lungs and translocation to the bone may be factors in the radiation dose pattern and the type and location of bone tumors that developed after inhalation of $^{238}PuO_2$.

In another study, Muggenburg et al. (1994) exposed 144 Beagle dogs to $^{238}PuO_2$ aerosols; 72 of these dogs inhaled monodisperse aerosols of $^{238}PuO_2$ with AMADs of 1.5 µm, and 72 dogs inhaled 3.0-µm AMAD particles. For each particle size, dogs were exposed to achieve one of the following six graded activity levels of initial lung burden: 0.57, 0.27, 0.14, 0.08, 0.03, or 0.01 µCi of $^{238}PuO_2$/kg. These dogs were observed for biological effects (cancerous and non-cancerous effects) over their natural lifespan. The $^{238}PuO_2$ aerosol exposures resulted in initial lung burden ranging from 37 to 0.11µCi and from 1.50 to 0.01 µCi (1.4–0.004 and 0.06–0.0004 MBq) of $^{238}PuO_2$/kg of body mass for the 1.5- and 3.0-µm particles, respectively. The particles were found to dissolve slowly, resulting in translocation of the Pu to liver, bone, and other tissue sites. The principal late-occurring effects were tumors of the lung, skeleton, and liver. Lung tumors were detected in 47 of the exposed dogs; within this group, lung tumors were the primary cause of death in 8 dogs that died from 3.6 to 12.3 years after exposure. Twenty-seven dogs that died from bone tumors also had lung tumors. Lung tumors were primarily bronchoalveolar carcinomas and papillary adenocarcinomas. Skeletal tumors were detected in 92 dogs; of this group, bone tumors were the primary cause of death in 89 dogs that died from 3.1 to 13.2 years after exposure. These tumors were primarily osteosarcomas that occurred in the axial skeleton and head of the humerus. Liver tumors were detected in 19 dogs and caused the death of 2 dogs that died from 6.6 to 13.2 years after exposure. Thirteen of these dogs had a variety of malignant liver tumors and 6 had only benign liver tumors. Risk factors estimated for these cancers were 2.8 lung cancers per $10^6$ dog-rad, 8.0 liver cancers per $10^6$ dog-rad, and 6.2 bone cancers per $10^6$ dog-rad.

Using a different isotope of Pu, Muggenburg et al. (1988) exposed 216 Beagle dogs to $^{239}PuO_2$ aerosols. The $^{239}PuO_2$ aerosols were monodisperse with AMADs of 0.75, 1.5, or 3.0 µm. After the inhalation was completed, all animals were matched by age and sex (6 males and 4 females in each group). Group I dogs had initial pulmonary burdens (IPBs) of 8.91–109.9 µCi (0.3–4 MBq) of $^{239}PuO_2$/kg of body mass with a mean of 42.9 µCi/kg (1.6 MBq/kg). Group II dogs had IPBs of 2.97–52.9 µCi (0.1–2 MBq) of $^{239}PuO_2$/kg

of body mass with a mean of 15.9 µCi/kg (0.6 MBq/kg). The plutonium particles produced protracted alpha irradiation of the lungs over the course of several years. The average alpha dose to the lungs to 2,600 days after exposure for the dogs in group I ranged from 230 to 3,200 rad and for the dogs in group II, 80 to 1,570 rad. Five dogs died within 1 year of exposure. Lung carcinomas were observed in 3 dogs (2 males and 1 female) from group I (2,900–3,200 rad) and in 1 dog (male) from group II (1,000 rad). These 3 dogs from group I had the highest doses and had many small, dense, parenchymal scars and small foci of alveolar septal fibrosis scattered throughout the lungs. Alveolar epithelial hyperplasia was associated with many of the fibrotic foci. Oral melanoma was found in one dog (male) from group II that died (190 rad).The authors note that these findings indicate that alpha irradiation of the lungs of humans could produce restrictive lung disease at long times after initial exposure. Other studies in dogs have demonstrated that exposure to $^{239}$Pu can induce lung cancer (Boecker et al. 1988; Galvin et al. 1989).

In addition to Pu, other radionuclides have been shown to induce cancer in dogs. Hahn et al. (1977) reported on a series of lifespan studies initiated to study the biological effects of beta emitters using aerosols of insoluble fused-clay particles containing $^{90}$Y, $^{91}$Y, $^{144}$Ce, or $^{90}$Sr. AMADs ranged from 0.8 to 2.7 µm and the duration of exposure was 2–48 minutes. $^{90}$Y exposures resulted in a range of initial lung burdens of 0 or 80–5,200 µCi/kg body weight; $^{91}$Y exposures resulted in a range of initial lung burdens of 0 or 11–360 µCi/kg; $^{144}$Ce exposures resulted in a range of initial lung burdens of 0 or 0.0024–210 µCi/kg; and $^{90}$Sr exposures resulted in a range of initial lung burdens of 0 or 3.7–94 µCi/kg. The approximate effective half-lives in the lungs of insoluble $^{90}$Y, $^{91}$Y, $^{144}$Ce, and $^{90}$Sr are 2.6, 50, 180, and 400 days, respectively. Dogs exposed to $^{144}$Ce or $^{90}$Sr generally had more active inflammation and pulmonary fibrosis than dogs exposed to $^{90}$Y or $^{91}$Y, perhaps due to their longer average survival time after inhalation exposure and the influence of the continuous irradiation. Primary malignant lung tumors were found in 5 of the $^{91}$Y exposed dogs (cumulative lung doses to death of 16,000–25,000 rad), 9 of the $^{144}$Ce exposed dogs (22,000–61,000 rad), and 14 of the $^{90}$Sr exposed dogs (34,000–68,000 rad). Several dogs died with primary hemangiosarcomas of the heart or mediastinum, and several died with primary bone tumors or epithelial tumors associated with the nasal cavity. Exposure to $^{144}$Ce or $^{90}$Sr, with dose rates that decreased slowly, induced pulmonary hemangiosarcomas. Pulmonary irradiation from $^{91}$Y, with a rapidly decreasing dose rate, resulted in bronchoalveolar carcinomas. Benjamin et al. (1978) exposed dogs to $^{144}$Ce in fused aluminosilicate particles with particle sizes ranging from 1.4 to 2.7 µm. Radiation pneumonitis and pulmonary fibrosis were evident in 13 of 14 dogs that died. Additionally, there was one bronchoalveolar-squamous carcinoma and four pulmonary hemangiosarcomas. The tumors observed

developed within a time period when the dogs showed severe lymphopenia and also were likely to have immune suppression. These studies suggest that chronic pulmonary irradiation from internally deposited radionuclides may have a dual effect in terms of combined carcinogenic and immunosuppressive effects.

Other species exposed to Pu isotopes show similar results. Brooks et al. (1992) exposed male monkeys by nose-only inhalation to an aerosol of soluble $^{239}Pu(NO_3)_4$ to produce projected initial lung burdens of either 1.08, 0.27, or 0.1 μCi (0.04, 0.01, or 0.004 MBq). Total skeletal plutonium activity was nearly constant for the first year after exposure; however, the skeletal burden at sacrifice increased with time up to 99 months after exposure to 1.08 μCi (0.04 MBq) because of transfer from other organs. $^{239}Pu$ in the liver peaked at 1 year and then decreased to about 10% of the peak value at 99 months postexposure. In the testes, Pu was localized in the interstitial tissue with only 0.01–0.002% of the projected lung burden remaining in the testes at 99 months after inhalation. Animals exposed to 1.08 μCi (0.04 MBq) died (3 of the 8) of radiation-related pulmonary pneumonitis and fibrosis, and a primary papillary adenocarcinoma of the lung was identified in one animal in that group. Of 2 animals exposed to 0.27 μCi (0.01 MBq), 1 developed fibrosis and 1 developed fibrosis and pneumonitis. Of those exposed to 1.08 μCi (0.04 MBq), 6 developed pneumonitis, 9 developed fibrosis, 7 developed alveolar epithelial proliferation, and 1 developed lung cancer. Overall, results of this study indicate that the lungs, the bone, and the liver are the major sites of deposition following inhalation of soluble plutonium in monkeys. The primary biological effects, pneumonitis and pulmonary fibrosis, were seen in monkeys with large initial plutonium burdens. There was little indication of chromosome damage at levels of plutonium at which there were no major histological changes in the lungs.

Hahn et al. (1987) exposed 16 male Rhesus monkeys to particles laden with $^{239}PuO_2$ via inhalation (AMAD 1.6 μm). Initial lung burdens ranged from 0.0018 to 1.8 μCi (0.00007–0.07 MBq). A pulmonary fibrosarcoma of bronchial origin was discovered in one monkey that died of pulmonary fibrosis after 9 years (3,277 days) with a radiation dose to the lungs of 1,400 rad (14 Gy). The fibrosarcoma proliferated around the major bronchus of the right cardiac lung lobe and extended into the bronchial lumen and surrounding pulmonary parenchyma. The time-dose relationship for survival is consistent with that of dogs and baboons that inhaled plutonium dioxide and died with lung tumors.

In addition to dogs and monkeys, induction of cancers in rats irradiated with different radionuclides has also been studied. A lifespan study was conducted by Lundgren et al. (1981) in CFW random-bred male

mice for the toxicity of $^{90}Y$ (AMAD 0.7–1.4 μm) inhaled in insoluble fused aluminosilicate particles. Groups of 25–393 mice were exposed to achieve initial lung burdens of 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and 61–140 μCi (0.04–0.4, 0.4–0.7, 0.8–1.1, 1.2–1.5, 1.5–1.8, 1.9–2.2, and 2.3–5.2 MBq). Exposures were 10–20 minutes. Control mice (n=763) were either unexposed, sham exposed, or exposed to nonradioactive Y in fused aluminosilicate particles. At death, animals were necropsied and major organs examined. Mean absorbed dose to the lungs to death were 1,100, 2,300, 3,800, 6,000, 7,200, 8,800, and 14,000 rad (11, 23, 38, 60, 72, 88, and 140 Gy) for initial lung burdens of 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and 61–140 μCi (0.04–0.4, 0.4–0.7, 0.8–1.1, 1.2–1.5, 1.5–1.8, 1.9–2.2, and 2.3–5.2 MBq), respectively. The cumulative survival rates of mice in groups with initial lung burdens up to 20 μCi (0.7 MBq) that produced lung doses as large as 2,300 rad (23 Gy) were not significantly different from that of controls. Larger lung burdens caused lung doses >3,000 rad (30 Gy) and resulted in radiation pneumonitis and a significant shortening of the lifespan ($p<0.05$). Median survival time ranged from 12% to 2.1% of controls at initial lung burdens of more than 20 μCi, and median time of survival after exposure ranged from 66 to 12 days for these dose levels. Radiation pneumonitis was observed in 75–100% of mice at these dose levels. The incidences of all lung tumors and other lesions in exposed mice were similar to those of controls, except for pulmonary adenomas, which were found more frequently in groups of mice with initial lung burdens of as large as 20 μCi (0.7 MBq). The early occurring biological effects observed in mice in this study were similar to those observed in Beagle dogs exposed to $^{90}Y$.

Hahn and Lundgren (1992) also studied lung cancers induced in rats by inhaled $^{144}CeO_2$. Rats were exposed once or repeatedly by inhaling $^{144}CeO_2$ and observed over their natural lifespan. Three groups (a total of 314 rats) were exposed once, briefly, to $^{144}CeO_2$ to achieve lung burdens of 0.06, 0.32, 1.16, or 6.48 μCi (0.002, 0.01, 0.04, and 0.24 MBq). Another group of 201 rats was repeatedly exposed briefly once every other month for 1 year (7 exposures) to initially establish and subsequently re-establish desired lung burdens in groups of 18–38 males and 19–38 females of 0.35, 1.30, 5.67, or 32.4 μCi (0.01, 0.05, 0.2, and 1.2 MBq). There was significant life shortening only in those rats exposed repeatedly at the highest radioactivity level (32.4 μCi, 1.2 MBq). In these rats, there was a high percentage of squamous cell carcinomas of the lungs, as well as much lower percentages of adenocarcinomas of the lungs, hemangiosarcomas of the lungs, and pleural mesotheliomas. At lower doses, adenocarcinomas were the predominant tumor, with alveolar, papillary, tubular, or undifferentiated adenocarcinomas most commonly observed histologically. The lung neoplasms induced by this beta-emitting radionuclide are

similar in nature to those induced by alpha-emitting radionuclides deposited in the lung in rats. However, the radiation-induced squamous cell carcinomas of the lungs differed from those induced by nonradioactive compounds.

Many other studies also confirm the formation of cancers of the respiratory tract in laboratory animals (Benjamin et al. 1975, 1978, 1979; Boecker et al. 1988; Gillette et al. 1992; Hahn et al. 1976, 1980, 1988; Lundgren et al. 1974, 1980a, 1983, 1991; McClellan et al. 1973).

Skin and bone cancer have been demonstrated after external exposure to radionuclides, particularly those that are beta and gamma emitters. Ootsuyama and Tanooka (1989) exposed female mice to beta irradiation from 40,000 µCi (1,500 MBq) of $^{90}$Sr and $^{90}$Y which delivered a surface dose rate of 228 rad/minute (2.28 Gy/min) and a 20–80% lower dose rate to the top of the vertebrae. Mice were irradiated three times weekly at skin entrance doses per exposure of 135, 150, 250, 350, 470, and 1,180 rad (1.35, 1.5, 2.5, 3.5, 4.7, and 11.8 Gy), respectively, and irradiation was continued until a palpable tumor appeared (up to 86 weeks). Tumors that formed in the irradiated area were of skin and bone origin. Most mice had either an osteosarcoma or a skin tumor, while some mice had both osteosarcomas and skin tumors. Osteosarcomas were induced most frequently with skin surface doses of 250–350 rad (2.5–3.5 Gy) per exposure. These doses were 20–80% lower at the depth of the bone. The skin is incidentally irradiated in the radiotherapy of deep tumors. Repetitive irradiation was essential, or at least more effective, for induction of osteosarcomas, as well as for skin tumors, and the carcinogenic dose for osteosarcoma was less than that for skin tumors.

Hulse (1966) irradiated female mice with $^{204}$Tl and then allowed them to live out their natural life (unless they were moribund or sacrifice was deemed necessary). Nominal doses ranged from 750 to 12,000 rad (7.5–120 Gy). $^{204}$Tl beta particles have a low energy (mean 0.24 MeV) and a maximum range in soft tissue of 3 mm. Doses to the dermis and epidermis were 69–72% and 40–70%, respectively, of the epidermal entrance dose. Mice were irradiated on one or two zones. The single-zone exposure included the middle of the trunk, and the two-zone exposure included the thorax (with proximal forelimbs) and pelvis (with hindlimbs), with an intervening unirradiated gap of about 1 cm. In one group, two zones were arranged to be immediately adjacent (thorax-midtrunk, midtrunk-pelvis) with the potential for slight overlap due to the movement of the mice. The percentage of mice irradiated on one zone only and dying with skin tumors was 7, 25, 42, and 57 for the 1,500-, 3,000-, 6,000-, and 12,000-rad (15, 30, 60, and 120

Gy) dose groups, respectively. In mice exposed to two separate zones, the percentage dying of skin tumors was 3, 17, and 50 for the 750-, 1,500-, and 3,000-rad (7.5, 15, and 30 Gy) dose groups, respectively. Mice that were irradiated on two adjacent zones received 1,500 rad (15 Gy) only. Twenty percent of these mice died with skin tumors. A total of 133 tumors arose in tissues which were affected by the irradiation, and 7 tumors arose in similar tissues outside the irradiated zones. There were 20 epidermal tumors: 2 benign and 18 squamous cell carcinomas, which were situated on the torso. There were 96 dermal tumors; 77 of those were malignant and of those 74 were fibrosarcomas. Five fibrosarcomas occurred beneath the irradiated skin and 12 breast tumors occurred. No tumors of the epidermis or dermis were seen in the unirradiated control mice. The maximum incidence of dermal tumors in all dose groups occurred during the third year after irradiation. Increasing the number of irradiated zones from one to two zones, which doubled the exposed skin area, essentially doubled the animal's chance of dying from skin cancer.

In summary, cancer is the major latent biological effect in several studies identified in this profile after inhalation, ingestion, or external exposure. Reports of cancer induction after ingestion and the more unconventional exposure routes are numerous (Evans et al. 1966; Martland 1931; Raabe 1994; Rowland et al. 1978; Speiss and Mays 1970). Excess cancer has been reported in humans after exposure to varying amounts of radiation during the Hiroshima and Nagasaki atomic blasts (Shimizu et al. 1988), which has provided risk assessors a unique data set to determine the short- and long-term biological effects of radiation in humans. Several other studies that monitored cancer death rates from radiation exposure in humans were also located (Checkoway et al. 1988; Kneale et al. 1981; Sorahan and Roberts 1993). Reports of humans receiving an acute inhalation, oral, dermal, or external dose of radiation under controlled conditions were not identified in the open literature. Levels of Significant Exposure to Radiation and Radioactive Material tables that describe Cancer Effect Levels (CELs) from exposure to radiation in humans and laboratory animals are provided in Chapter 8 of this profile.

Many laboratory animal inhalation exposure studies were identified that described increased incidences of cancer developing in a variety of species after exposure to alpha, beta, and gamma radiation. Many of these studies were selected for discussion in this profile because they were lifespan studies, concentrating on the effects of alpha ($^{238}$Pu, $^{239}$Pu) and beta ($^{90}$Sr, $^{144}$Ce, $^{91}$Y, $^{137}$Cs) emitters. The main animal model, the Beagle dog, has lungs that are similar anatomically, physiologically, and morphologically to human lungs, making them an ideal lung model to study the potential effects of inhaled nuclides in humans. The nasopharageal structure of the Beagle is significantly different from a human's; therefore, comparisons of nasal tissue and bone cancers between the species are not practical at this time. These studies provide

valuable data on the long-term toxicity of many radionuclides that would be likely to be inhaled in soluble and insoluble forms during a nuclear fallout or an acute exposure event, as well as low-level radionuclide exposure from fallout and natural in the atmosphere. Biennial reports of these lifespan studies that summarize the most recent findings from these laboratory animal studies are available.

These animal studies, especially the Beagle dog studies, clearly demonstrate that the inhalation of very large amounts of radionuclides in soluble or insoluble forms, which results in very high absorbed doses to the lungs, has the potential to produce lung cancer and to induce cancers in other organs. These cancers are the same cancers that would normally appear with a lower frequency in an unexposed animal population. After exposure(s) to one or to a combination of radionuclides, the incidence of these naturally occurring cancers tend to increase, though the latent periods do not change. This observation was demonstrated by the studies performed by many investigators in which $^{238}PuO_2$ and $^{239}PuO_2$ exposed dogs had increases in lung, skeletal and liver tumors after exposures to varying doses of these nuclides (Boecker et al. 1988; Brooks et al. 1992; Gillett et al. 1985; Hahn et al. 1987, 1981; Muggenburg et al. 1994). This trend, also noted with the cancers that were produced in those individuals exposed to external sources of ionizing radiation after the atomic blasts in Hiroshima and Nagasaki, Japan, in August 1945, is discussed in more detail below (Shimizu et al. 1988).

The sites where these cancers occurred in exposed laboratory animals depended largely on (1) the dose, which depends on the quantity of radioactive material, (2) the physical properties of the particle (or vapor) they were incorporated into, (3) the solubility of the particle, (4) the particle size, and (5) the radiological and biological properties of the material. For example, for dogs exposed to insoluble aerosols of $^{238}Pu$ (1.5 and 3.0 μm), it may be reasonably surmised that these animals would develop lung tumors based on the physical half-life of the radionuclide, the insoluble nature of the particle, the small particle size (long retention times), the dose, and the tissues at risk of receiving large doses of radiation within a short distance of the particle retention site. Lung tumors did in fact develop in these animals at an increased incidence rate many years after the initial exposure. Liver and bone tumors also developed in conjunction with some of these lung tumors. Over a period of time, the particles slowly dissolved and the $^{239}Pu$ was transferred to the hepatic and skeletal tissues, subsequently irradiating other susceptible tissues and inducing cancers of the liver and osteosarcomas of the bone (Muggenburg et al. 1994). Metastasis also is a factor in the appearance of cancer in some organs.

External exposure has also been found to induce cancers in both humans and laboratory animals. A few human studies that involved external exposures to radiation and resulted in cancer were identified, but the best study available to date is the Life Span Study (LSS) currently being conducted by the Radiation Effects Research Foundation (RERF) with the survivors of the atomic bombings of Japan in 1945. A large database is available from the persons exposed to radiation from the atomic bombing of Hiroshima and Nagasaki. According to DS86 doses, the major type of radiation was gamma emissions, with lesser amounts of neutron radiation than originally anticipated using T65D dosimetry assumptions; the estimates of doses to these individuals are still being refined today. Exposures are considered to be mostly from external radiation, with much smaller amounts of internal radiation from inhalation and oral exposure routes, due to relatively little fallout from those atomic blasts. In Nagasaki, however, survivors were exposed to the "Black Rain," which is fallout radioactivity mixed in a rain shower. Many of these individuals received high doses to their unprotected skin and even to skin under water-saturated clothing due to the high-activity, beta and gamma-emitting fission products. This ongoing epidemiologic study provides an excellent source of data for use in studying the delayed effects of radiation in humans.

As with cancers induced after inhalation of radioactive material by laboratory animals, cancers in humans or animals exposed to external radiation do not appear immediately after the initial exposure. In the Hiroshima and Nagasaki atomic bombing survivors, and in the dog studies discussed above, there was no dose-dependent shortening of the latent periods for cancer induction, except possibly for those individuals exposed to radiation within the first 10 years of life (which was dose-dependent). This observation may reflect a higher sensitivity to the effects of radiation in very young humans. Cancers were also of the type that are normally found in unexposed individuals, but they occurred with some increasing frequency. These cancers occur only when those individuals reach an age when these cancers normally would be expected to develop (except for leukemia). For example, a female #10 years of age who was exposed to external gamma radiation from the atomic blast and survived the acute effects of the initial radiation exposure would have an increased probability of developing (and dying from) breast cancer as a result of the latent radiation effects, but not before she reached the age at which the majority of unexposed women would be expected to start developing this specific cancer. The same would be true for the other types of cancers as well, except for leukemias. Deaths due to leukemia did exhibit a minimum latent period (2–3 years). The incidence of the cancer increased to a peak at 6–8 years after exposure and the incidence declined after that. A slightly significant increase in deaths due to leukemia existed at least through 1980

(the cut-off date for much of the DS86 dosimetry system data), some 35 years after the initial exposure; this increase was independent of the age at which the initial exposure had occurred.

In another report by Upton (1991) and in the report by Shimizu et al. (1988), the same cohort was reported to show linear dose-mortality relationship responses for cancers (other than leukemia) ranging from 40 to 300 rad (0.4–3 Gy). In the most recent report on this cohort, solid cancer excess deaths increased greatly in the last 5-year study period, 1986–1990; for those exposed as children, 50% of the excess deaths occurred during this period (Pierce et al. 1996). For all cancers, most of the excess deaths were due to leukemia and most leukemias occurred in the 15 years following exposure. Though excess relative risk for those exposed as children declined over the recent years, the excess absolute risk increased rapidly and excess absolute risk is seen to be an important measure of radiation's population impact. Solid cancer excess lifetime risk per sievert was estimated at 0.10 for males (10 cancers per 100 people) and 0.14 for females, and still shows a linearity up to about 3 Sv (Pierce et al. 1996). However, leukemia showed nonlinearity of risks: risk at 0.1 Sv was 1/20 of the risk at 1 Sv.

Cancer mortality due to ionizing radiation has been evaluated extensively (BEIR V 1990; Shimizu et al. 1988; Upton 1991). In summary, for the Japanese atomic bomb survivors, the relative risk for the whole exposed population (all ages and both sexes) for malignant neoplasms (including leukemia) for the years 1950–1985 has been estimated to be 1.39 (range 1.32–1.46) per 100 rad (1 Gy), corresponding to an absolute risk of 13.1 (10.1–15.9) excess deaths per million person rad ($10^4$ person-Gy)/year. When leukemia is excluded from the previous estimates, the relative risk for the whole exposed population (all ages and both sexes) for solid cancers is estimated to be 0.41 (0.32–0.51) per 100 rad (per Gy) organ-absorbed dose, corresponding to a lower absolute risk of 10.13 excess cancer deaths per million person rad ($10^4$ person-Gy)/year organ-absorbed dose. When total cancer mortality (including leukemia) is reexamined on the basis of sex, sex ratios of radiation-induced cancers at specific sites are not significantly different from those of the unexposed general population. The relative risk for some epithelial tumors tends to be somewhat higher in females than in males (Upton 1991). Finally, when the data are re-examined as to cancer mortality and age at exposure, the current data suggest that the lifetime risk of developing radiation-induced cancer is substantially lower in those persons exposed during their adult years than in those exposed during childhood or adolescence, a conclusion supported by BEIR V (1990). Several types of

cancer were observed with increased frequencies in this exposed population and are summarized in Table 3-8.

CELs from exposure to ionizing radiation in humans and laboratory animals are summarized in the Levels of Significant Exposure to Radiation and Radioactive Material tables in Chapter 8 of this profile.

## 3.3 IDENTIFICATION OF DATA NEEDS

The database appears to have a sufficient volume of information for regulators to allow workers to work safely with radiation sources. This is verified by the fact that the nuclear power industry has the best overall safety record of all industries. This good safety record, with a Standardized Mortality Ratio (SMR) of less than 100 is usually attributed to the "Healthy Worker Effect." However, for scientific reasons, the following have been identified as potential data needs regarding health effects that may be associated with exposure to ionizing radiation:

- Since somatic and reproductive cell chromosomes are radiosensitive tissues that can sustain damage after exposure to ionizing radiation, damage to the chromosomes and the genes on them in exposed populations has potentially serious implications. Better methods are needed by which to estimate the levels of exposure to ionizing radiation that may result in an increased risk of hereditary disease.

- Important gaps in knowledge should be filled to permit more reliable estimation of genetic and hereditary risks. In some cases this might include collection of new data that could remove or refine assumptions needed in the direct and indirect (doubling-dose) methods of hereditary risk estimation. In other cases, gaps in knowledge could be filled by the reevaluation of the masses of data collected in the past (for example, specific-locus experiments) in the light of new understandings about hereditary risk. In addition, information gathered as part of the Human Genome Project may lead to improvements in the existing methods or to entirely new methods of estimating hereditary risk.

- The largest group of workers that receive elevated doses of ionizing radiation are airline air crews. Assuming a dose of 1 mrem/hr (0.01 mSv/hr) and 72–100 hours/month airtime for 11 months, this leads to an approximate dose of 800–1,100 mrem/year (8–11 mSv/year), about twice the annual dose of an average nuclear power plant worker. There is a need to determine whether or not this long-term, continuing, low-level radiation dose rate leads to harmful effects.

- The mechanisms by which cancer is induced in living cells are complex and an area under intense study. More research is required to better understand the mechanisms by which cancer is induced after exposure to chemical carcinogens and to ionizing radiation. This would include the identification of unique biomarkers and biochemical pathways at the cellular and tissue level, and the study of radiological and chemical mixtures.

- Regarding radon exposure, several studies involving underground-miner surveys need to be completed and the data analyzed for the interaction between radon and smoking. These studies should also provide more information on radon dosimetry and narrow some uncertainties in applying the lung-cancer risk data derived from the miner data sets to estimation of risk of radon exposure in the general population.

- Epidemiological studies need to continue in order to more firmly describe the risks of lung cancer in underground miners and the risks of indoor home radon exposure to those potentially exposed to radon and radon progeny. In addition, adding a thoron ($^{220}$Rn- and $^{220}$Rn- plus decay products) study to the radon studies would be of benefit, because thoron is hard to get into the home. If it does, the decay products are long-lived; there are limited data on in-home thoron and thoron decay product levels.

- Further modeling of the indoor air environment is needed to assess potential health consequences of indoor radon exposure.

- The role of $^{210}$Po in tobacco smoke and lung cancer should continue to be evaluated; this includes bronchial and lung dosimetry, identification and characterization of target cells, and the role of cofactors in the carcinogenic response.

- The deterministic acute and delayed health effects from $^{210}$Po, particularly those affecting the renal, cardiovascular, and reproductive systems, should continue to be investigated.

- More quantitative information regarding the $^{224}$Ra, $^{226}$Ra, and $^{228}$Ra human exposures is needed to more adequately evaluate the magnitude of some dosimetric uncertainties and what impact these uncertainties have on quantitative risk estimation.

- The bone cancer information from all of the human $^{224}$Ra, $^{226}$Ra, and $^{228}$Ra exposures should be integrated and more adequately analyzed.

- Research should continue on identifying the cells at risk after exposure to radium. This should include cell behavior over time, changes in cell behavior, location of cells in relation to the microenvironment of the radiation field, responses of the cell to the radiation, and the time course and distribution of radioactivity in the bone.

- The dosimetry of the mastoids should be examined in order to calculate the risk per unit of epithelial tissue and per unit of cell dose.

- Data should be obtained from the five major epidemiological studies of Thorotrast-exposed patients and the data analyzed to develop risk models for liver and other cancers.

- The dosimetry of the thorium isotopes at the cellular level in target organs should be closely examined.

- The mechanism of uranium deposition and redistribution in bone should be further investigated in order to more accurately define the potential carcinogenic effect of natural uranium based on results obtained from enriched uranium or other alpha particle emitters.

- The current epidemiological studies of worker populations exposed to transuranic elements should be continued.

- The current lifespan studies with dogs should be completed and the results reported.

- The current lifespan studies of the Japanese atomic bomb survivors should be continued and the results reported regularly every 5 years.

- Studies should continue regarding the genetic effects of low-level exposure to ionizing radiation, particularly in the second generation offspring of the Japanese atomic bomb survivors. Better methods for extrapolating data from animal studies for applications in human genetic risk assessment are also needed.

- It would be useful to have some information on induced dominant damage in female mice for use in the direct method of hereditary risk estimation, as none has been known to have been collected. Presently the application of the direct method to females assumes that the relative risks of the sexes are the same for serious dominant mutations as they are for specific-locus mutations, which are recessives.

- Efforts to assess the carcinogenic risks of exposure to low levels of ionizing radiation, for both single dose and protracted and fractioned doses, should continue.

- The carcinogenicity of neutron radiation exposure in human populations should continue to be examined. Similarly, the mutagenicity of low doses of neutron radiation should continued to be investigated in order to more comfortably predict the potential genetic risks observed in laboratory animals and extrapolate those findings to human populations.

## 3.4 CONCLUSIONS

This chapter has provided an overview of the health effects related to ionizing radiation exposure in humans and laboratory animals. These effects can be both non-carcinogenic and carcinogenic in nature. Non-carcinogenic effects primarily result in immediate effects, mainly to organs with rapidly dividing cells, which include the hematopoietic system, gastrointestinal tract, and skin, or delayed effects such as cataracts and embryo/fetal development problems. Carcinogenic effects also may occur in any number of organ systems. This end point may not be expressed for several years after the initial exposure. The dose-response relationships for these effects are known from the massive amount of data from studies on both humans and animals. Epidemiology studies are not likely to provide significant refinement of radiation risk estimates. The most fruitful approach to further understanding risk from exposure to ionizing radiation is through molecular studies, including the identification of unique biomarkers and pathogenic pathways at the cellular and tissue levels.