3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of strontium. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile. Appendix D contains background information on radiation physics, chemistry, and biology.

Naturally occurring strontium is a mixture of four stable (nonradioactive) isotopes, ^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr, the last being the most abundant. Section 3.2 contains a discussion of the chemical toxicity of stable strontium; radiation toxicity associated with exposure to radiostrontium (primarily ^{90}Sr and ^{89}Sr) is discussed in Section 3.3. The chemical properties of stable and radioactive strontium isotopes are identical and are described in Chapter 4.

Strontium is fairly reactive and therefore is rarely found in its pure form in the earth's crust. Examples of common strontium compounds include strontium carbonate, strontium chloride, strontium hydroxide, strontium nitrate, strontium oxide, and strontium titanate. The most toxic strontium compound is strontium chromate, which is used in the production of pigments and can cause cancer by the inhalation route. Strontium chromate is not included in the Levels of Significant Exposure (LSE) tables for strontium since the carcinogenic effects of the compound are a function of the concentration of hexavalent chromium, and strontium only contributes to solubility. The Toxicological Profile for Chromium (Agency for Toxic Substances and Disease Registry 2000) should be consulted for additional information on the health effects of strontium chromate.

There is no direct evidence that strontium is toxic to humans, but there is suggestive epidemiological evidence that the oral toxicity observed at high doses in juvenile laboratory animals may pertain to humans under special circumstances. Stable strontium is of relatively low toxicity. It comprises about 4.6 ppm by weight of the human body, but does not have any recognized essential biological role. Human exposure to strontium is primarily by the oral route (via fruits, vegetables, and drinking water),

although inhalation exposures are also possible. No toxic effects of stable strontium have been reported for the exposure levels normally encountered in the environment. Strontium is not readily absorbed through intact skin, but is absorbed through abraded skin and through puncture wounds. The biological effects of strontium are related to its chemical similarity to calcium, with both elements being found in Group 2 of the periodic table and forming divalent cations. However, since strontium is not the same size as calcium, it does not substitute precisely for calcium in biological processes. At different stages of the life cycle, organisms vary in their ability to discriminate between strontium and calcium, which may cause age-related differences in gastrointestinal absorption, and therefore in health effects. Because of its similarity to calcium, strontium accumulates to a high degree in bone, and, in high concentrations, may seriously interfere with the normal process of bone development. The young are particularly vulnerable because a lack of discrimination between calcium and strontium occurs during a dynamic period of bone formation and growth. For this reason, body burdens of strontium will be higher in children than in adults, and the health effects associated with high exposure levels would be more severe. As suggested in one human study and demonstrated in several animal studies, strontium 'rickets' is one potential consequence of childhood exposure to excess stable strontium.

Beta emissions from ^{90}Sr have a limited ability to penetrate through tissue (see Appendix D Section D.2.3). For that reason, radiostrontium must be internalized or placed in close contact with skin before adverse health effects will occur. The 'bone-seeking' behavior of strontium is the basis for concern regarding oral or inhalation exposures to the radioactive isotopes, particularly ^{90}Sr, with its long half-life of 29 years and highly energetic 0.546 MeV beta particles, plus the 2.2 MeV beta particles of its short-lived ^{90}Y decay product isotope. Radioactive strontium isotopes incorporate into bone and irradiate the bone cells, the hemopoietic bone marrow, and potentially, the soft tissues surrounding bone, especially in the skull. Human populations accidentally exposed to high levels of radiation from radiostrontium (and other radionuclides and external radiation) experienced chronic radiation sickness (postirradiation changes in hematological parameters) and increased leukemia and cancer mortality in the decades following exposure. In animal studies, high-level exposures to ^{90}Sr led to death within weeks because of radiation damage to hemopoietic tissues. Longer-term lower level exposures that overcome genetic repair mechanisms may lead to myeloid leukemia, osteosarcoma, and lymphoma (only observed in some rodent studies). It should be understood that because strontium is retained for a long time in the skeleton, acute- or intermediate-duration uptakes (i.e., absorption events occurring within a period of <2 weeks or <1 year, respectively) can result in decade-long (i.e., chronic) effects from internal exposure to the radiation emitted from the retained isotopes. Children would appear to have a higher lifetime risk for cancer effects per unit uptake, because of their relatively higher rate of skeletal incorporation of

strontium and potentially longer radiation exposure period. Immediately nonlethal exposures to high levels of radioactive strontium may contribute to suppression of the immune system.

Limited human data are available regarding health effects that can be exclusively associated with exposure to radioactive strontium sources such as ^{90}Sr and ^{89}Sr. These radionuclides are products of nuclear fission and may, therefore, be released from sites where nuclear fission occurs, from radioactive material removed from such sites, or from leakage of radioactive strontium sources. Both ^{90}Sr and ^{89}Sr emit beta radiation that travels short distances and can penetrate the skin and superficial body tissues. The radiation dose from these radionuclides can be classified as either external (if the source is outside the body) or internal (if the source is inside the body).

The external dose from strontium radionuclides emitting beta radiation outside the body is normally of little health concern unless the radioactive material contacts the skin. Skin contact can allow the beta radiation to pass through the epidermis to live dermal tissue where it becomes a major contributor to a radiostrontium-generated radiation dose to the skin. At very high doses, the beta radiation can cause such adverse effects as erythema, ulceration, or even tissue necrosis.

Once radioactive strontium is internalized, it is absorbed, distributed, and excreted in the same manner as stable strontium; the chemical similarity of strontium to calcium results in deposition of radioactive strontium in bone. The internal radiation dose from strontium is actually a measure of the amount of energy that the beta emissions deposit in tissue. The short-range beta radiation produces a localized dose, generally to bone and the soft tissues adjacent to bone; hemopoietic bone marrow is the most biologically significant target of radioactive strontium emissions. Molecular damage results from the direct ionization of atoms that are encountered by beta radiation and by interactions of resulting free radicals with nearby atoms. Tissue damage results when the molecular damage is extensive and exceeds the capacity of natural repair mechanisms.

In radiation biology, the term *absorbed dose* is the amount of energy deposited by radiation over time per unit mass of tissue, expressed in units of rad or gray (Gy) (see Appendix D for a detailed description of principles of ionizing radiation). The term *dose equivalent* refers to the biologically significant dose, which is determined by multiplying the absorbed dose by a quality factor for the type and energy of the radiations involved. Dose equivalent is expressed in units of rem or sievert (Sv). The quality factor is considered to be unity for the beta radiation emitted from ^{90}Sr and ^{89}Sr, so for these radionuclides, the absorbed dose (in rad or gray) is numerically identical to the dose equivalent (in rem or sievert). The dose

equivalent from internalized strontium radionuclides is estimated using the quantity of material entering the body (via ingestion or inhalation), the biokinetic parameters for strontium (retention, distribution, and excretion), the energies and intensities of the beta radiation emitted, and the parameters describing the profile of absorbed radiation energy within the body. If, for example, a person ingests a given activity of radiostrontium (measured in curies [Ci] or becquerels [Bq]), the tissues of the body will absorb some of the energy of the emitted beta radiation in a pattern reflecting the kinetics of distribution and elimination of the ingested radiostrontium, the rate at which the radioactive isotope decays to a stable form, and the age of the person at the time of ingestion (which affects both the biokinetics of the radiostrontium and the potential length of time over which the tissues can be exposed to the radiation). Each tissue, therefore, can receive a different dose equivalent. The total dose equivalent for the body will reflect the integration of the dose equivalents for the various tissues using a weighting scheme for the relative sensitivities of tissues and organs.

The EPA has published a set of internal dose conversion factors for standard persons of various ages (newborn; 1, 5, 10, or 15 years of age; and adult) in its Federal Guidance Report No. 13 supplemental CD (EPA 2000e). For example, the EPA has estimated that the dose equivalents following ingestion of 1 Bq of ^{90}Sr are 2.77×10^{-8} and 2.77×10^{-7} Sv, respectively, for the adult and infant (assuming an integration time of 50 years for an adult following the initial exposure). For ^{89}Sr, these values are 2.57×10^{-9} Sv and 3.59×10^{-8} Sv, respectively. Age-specific dose coefficients for inhalation and ingestion of any of the radioactive isotopes of strontium by the general public can be found in ICRP publications 71 (ICRP 1995) and 72 (ICRP 1996), respectively. Dose coefficients for inhalation and ingestion of strontium radionuclides can be found in U.S. EPA Federal Guidance Report No. 11 (EPA 1988). Dose coefficients for external exposure to radioisotopes of strontium in air, surface water, or soil contaminated to various depths can be found in U.S. EPA Federal Guidance Report No. 12 (EPA 1993b).

Unless otherwise stated, exposure levels in the text are presented per kg of body weight. In Appendix D, standard and SI units of radiation activity (curies, becquerels) and absorbed dose (rad, gray) are compared in Table D-5 and are discussed in Sections D.2.2 Half-Life and Activity and D.3.1.2 Absorbed Dose and Absorbed Dose-Rate.

3.2 DISCUSSION OF HEALTH EFFECTS OF STABLE STRONTIUM BY ROUTE OF EXPOSURE

Section 3.2 discusses the chemical toxicity of strontium. Radiation toxicity resulting from exposure to radiostrontium is discussed in Section 3.3.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no

adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of strontium are indicated in Tables 3-2, 3-3, and 3-4 and Figures 3-2 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-2 and 3-3 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for strontium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

The only studies located regarding death in humans following inhalation exposure to stable strontium are related to strontium chromate. Strontium chromate has been implicated as a cause of increased deaths from lung cancer in occupational studies (Davies 1979, 1984) (see Section 3.2.1.7). The toxicity of strontium chromate is attributed to hexavalent chromium ion, which enters lung cells and is metabolized to a genotoxic agent. Strontium itself contributes to solubility of strontium chromate, but any associated health effect is expected to be masked by that of the chromate. No studies were located regarding death in animals following inhalation exposure to stable strontium.

3.2.1.2 Systemic Effects

No data are available regarding systemic effects following inhalation exposure to stable strontium for which the exposure levels are known. For that reason, no LSE table has been created for stable strontium. No studies were located that described gastrointestinal, hematological, hepatic, renal, body weight, metabolic, endocrine, dermal, or ocular effects in humans or animals following inhalation exposure to stable strontium.

Respiratory Effects. The only report of adverse respiratory effects in humans resulting from the inhalation of stable strontium is a case report of an anaphylactic reaction to smoke from an ignited roadside flare (Federman and Sachter 1997). The flare contained approximately 75% strontium nitrate (31% strontium), among other known irritating ingredients, and the exact contribution of strontium to the effect is uncertain. The anaphylactic reaction to the smoke included coughing, wheezing, and severe respiratory difficulties. This case report is discussed in Section 3.2.1.3 Immunological and Lymphoreticular Effects. No other reports were located describing longer-term respiratory effects following inhalation of stable strontium compounds by humans or animals.

Cardiovascular Effects. A single study documented adverse cardiovascular effects in humans resulting from the inhalation of stable strontium in smoke from an ignited roadside flare (Federman and Sachter 1997). Extreme tachycardia resulted as part of an anaphylactic reaction to the smoke, which contained ~31% strontium as strontium nitrate, in addition to other known irritants. The role of strontium

in this reaction is not established. No other reports were located describing longer-term cardiovascular effects following inhalation of stable strontium compounds by humans or animals.

3.2.1.3 Immunological and Lymphoreticular Effects

The single located study of immunological effects in humans following inhalation exposure to stable strontium is a case report of an anaphylactic reaction to smoke from an emergency roadside flare (Federman and Sachter 1997). A 35-year-old female paramedic developed a sudden, severe reaction upon inhaling fumes from a flare that contained approximately 31% strontium as strontium nitrate. Initial symptoms included coughing, wheezing, and shortness of breath that was not responsive to albuterol, epinephrine, or steroids; recovery ultimately required sedation, intubation, and intensive care for several days. Although the paramedic had been unsymptomatic before the incident, her medical history included several significant contributory factors: rheumatic fever requiring penicillin prophylaxis until age 12, a severe anaphylactic reaction to a bee sting at age 23, and adult-onset asthma at age 32. The ingredients of the flare (Road Fusee®; Standard Fusee Corporation, Easton, Maryland) included ±75% strontium nitrate (~31% strontium), ±10% potassium perchlorate, ±10% sulfur, and ±10% sawdust/oil binder. Upon combustion, each of these would yield products known to be irritating to the respiratory tract: strontium oxide, nitrous oxide, potassium oxide, chlorine gas, sulfur dioxide, and particulates. Thus, the exact contribution of strontium to the development of anaphylaxis in this case is uncertain. However, see Section 3.6.2 for a possible mechanism by which strontium could contribute to an immunological effect. No studies were located regarding immunological effects in animals following inhalation exposure to stable forms of strontium.

No studies were located regarding the following effects in humans or animals following inhalation exposure to stable strontium:

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

There were no reports regarding cancer in humans or animals resulting from inhalation exposure to stable strontium compounds except for strontium chromate. In an epidemiological study, no excess risk for lung cancer was found among workers in two Japanese factories who were involved in the production of strontium chromate pigment (Kano et al. 1993). However, exposures to strontium chromate in the factories may have been low because of suitable industrial hygiene procedures. Another epidemiological study examined workers in British chromate pigment manufacturing plants (Davies 1979, 1984). In one factory, both lead and zinc chromate were produced until 1976, and strontium chromate was produced from 1950 to 1968. For lung cancer deaths in workers exposed to 'high' and 'medium' levels of chromates before 1961, when industrial hygiene improvements were introduced, the observed/expected ratio (O/E) was 6/1.61, with a standard mortality ratio (SMR) of 373 ($p<0.01$). For workers exposed to 'high' and medium' levels from 1961 to 1967, the values were O/E=5/089, SMR=562 ($p<0.01$). The contribution of strontium to toxicity in these studies was not addressed.

No standard inhalation study of strontium chromate in animals was located. However, Levy et al. (1986) used an intrabronchial pellet implantation technique to evaluate the carcinogenicity of 23 different commercially available chromates, including two batches of strontium chromate. Metal pellets were coated with a mixture of cholesterol and strontium chromate and implanted into the left bronchus of male and female young rats (100 per group). Of 198 lungs treated with strontium chromate, 105 (53%) had a primary keratinizing squamous carcinoma of the bronchial epithelium. The authors indicated that carcinogenicity was associated with sparingly soluble hexavalent chromium compounds such as strontium, calcium, or zinc chromates.

3.2.2 Oral Exposure

There are no direct dose-response data for adverse effects of exposure to stable strontium in humans, but one epidemiological study suggests that the skeletal toxicity observed at high oral doses in juvenile animals may be relevant to humans (see Musculoskeletal Effects). At low exposure levels, ingestion of stable strontium poses no harm to organisms with access to adequate calcium, phosphorus, and vitamin D. At higher exposure levels, especially under conditions of inadequate calcium, phosphorus, and vitamin D, stable strontium will interfere with normal bone development, causing 'strontium rickets' of variable severity.

3.2.2.1 Death

No deaths in healthy humans have been reported after oral exposure to stable strontium. Stable strontium caused death in laboratory animals only at doses that are very high compared to normal human exposure. In acute exposure studies in mice, the oral LD_{50} for strontium nitrate was reported to be 2,350 mg strontium/kg in males (Llobet et al. 1991a). For strontium chloride administered by gavage, the acute oral LD_{50} in albino mice was reported to be 2,900 mg strontium/kg for males and 2,700 mg strontium/kg for females (Ghosh et al. 1990).

In intermediate-duration animal studies, ingestion of excess stable strontium resulted in increased mortality. The premature death rate was 40% among weanling male Sprague-Dawley rats fed stable strontium (form not specified) at a dose level of 565 mg strontium/kg/day for 43 days (Johnson et al. 1968). Weanling male Wistar rats exposed to strontium phosphate in the diet at a dose level of 2,820 mg strontium/kg/day for 4–6 weeks had a mortality rate of 30%, but no mortality occurred at 580 or 1,270 mg strontium/kg/day (Kshirsagar 1976). From an analysis of a pair-fed group (food intake matched to the high-dose group), the author concluded that the increased mortality in the high-dose group was not related to reduced food intake, but rather to the ingestion of strontium. No studies were located regarding death in animals following chronic-duration oral administration of stable strontium.

All reliable LOAEL values for death from stable strontium in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

No studies were located regarding dermal or ocular effects in humans or animals following oral exposure to stable strontium. The highest reliable NOAEL and all LOAEL values for the systemic effects from oral exposure to stable strontium in each species and duration category are shown in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to stable strontium. No studies were located regarding acute or chronic respiratory effects in animals following exposure to stable forms of strontium. In one intermediate-duration study, respiratory difficulties were noted in rats following lethal ingestion of 565 mg strontium/kg/day of stable strontium

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral

Key to figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Mouse (albino)	once (GW)				2900 M (LD50) 2700 F[c] (LD50)	Ghosh et al. 1990 Strontium chloride
2	Mouse (NS)	NR (NS)				2350 M (LD50)	Llobet et al. 1991a Strontium nitrate
	Systemic						
3	Rat (Wistar)	2 wks ad lib (F)	Hemato	110			Kroes et al. 1977 Strontium chloride 6H2O
			Musc/skel	110			
			Hepatic	110			
			Renal	110			
			Bd Wt	110			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
4	Rat (Wistar)	2 wks ad lib (F)	Gastro		3000 M (small intestine: decr acid & alkaline phosphatase; reversible)		Kshirsagar 1976 Strontium phosphate
			Musc/skel		3000 M (bone: incr alkaline phosphatase; reversible)		
			Hepatic		3000 M (incr alk phosphatase, decr acid phosphatase; reversible)		
			Bd Wt			3000 M (bd wt gain decr 62%)	
	INTERMEDIATE EXPOSURE						
	Death						
5	Rat (Sprague-Dawley)	PND 21-64 ad lib (F)				565 M (40% mortality)	Johnson et al. 1968 (NS)
6	Rat (Wistar)	4-6 wks ad lib (F)				2820 M (30% mortality)	Kshirsagar 1976 Strontium phosphate

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
7	Rat (Sprague-Dawley)	8 wks ad lib (W)	Musc/skel	168 M			Grynpas et al. 1996 (NS)
			Bd Wt	168 M			
			Metab	168 M			
8	Rat (Sprague-Dawley)	PND 21-64 ad lib (F)	Resp			565 M (unspecified difficulties)	Johnson et al. 1968 NS
			Musc/skel			565 M (rickets)	
9	Rat (Wistar)	90 d ad lib (F)	Hemato	166 F			Kroes et al. 1977 Strontium chloride 6H2O
			Musc/skel	166 F			
			Hepatic	166 F			
			Renal	166 F			
			Bd Wt	166 F			
			Metab	166 F			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
10	Rat (Wistar)	4-6 wks ad lib (F)	Cardio			2820 M (hemorrhage)	Kshirsagar 1976 Strontium phosphate
			Gastro	580 M	1270 M (small intestine: reversible decr alkaline phosphatase)		
			Musc/skel	580 M	1270 M (bone: incr alkaline phosphatase, reversible)		
			Hepatic	1270 M	2820 M (reversible decr alkaline phosphatase)		
			Bd Wt	580 M	1270 M (reversible decr in wt gain)		
11	Rat (Sprague-Dawley)	9 wks ad lib (W)	Musc/skel	524 M	633 M (bone calcification rate decr by 17%)		Marie et al. 1985 Strontium chloride
			Bd Wt	633 M			
			Metab	633 M			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
12	Rat (Wistar)	4 wk ad lib (F)	Musc/skel			1970 M (tibiae: length decr 33%, epiphyseal plates 5 x wider, decr mineralization)	Matsumoto 1976 Strontium carbonate
			Bd Wt			1970 M (bd wt gain decr by 60%)	
13	Rat (Wistar)	27 d ad lib (F)	Gastro	102	510 F (20% decr net intestinal Ca2+ absorption)		Morohashi et al. 1994 Strontium carbonate
			Musc/skel	102	510 F (decr bone formation, resorption, Ca2+ content of bone)		
			Bd Wt	510 F			
			Metab	102 F	510 F (hypocalcemia)		
14	Rat (Sprague-Dawley)	3 wk ad lib (F)	Musc/skel		500 M (abnormal bone mineralization)		Neufeld and Boskey 1994 Strontium carbonate
			Bd Wt	500 M			
			Metab	500 M			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Rat (England Wright Y)	PND 21-41 ad lib (F)	Musc/skel			1850 M (epiphyseal cartilage histopathology)	Reinholt et al. 1984 (NS)
			Bd Wt			1850 M (28% decr bd wt gain)	
			Metab	1850 M			
16	Rat (NS)	20 d ad lib (F)	Musc/skel	140[b] F	550 F (tibial epiphyseal cartilage abnormally wide)		Storey 1961 Strontium carbonate
			Bd Wt	1460 F		2220 F (24% decr bd wt gain)	
			Metab	4975 F			
17	Rat (NS)	20 d ad lib (F)	Musc/skel	690 F	1370 F (tibial epiphyseal cartilage abnormally wide; incr metaphyseal osteoid)		Storey 1961 Strontium carbonate
			Bd Wt	2750 F			
			Metab	2750 F			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
18	Rat (NS)	up to 7 months ad lib (F)	Musc/skel			2160 (rickets)	Storey 1962 Strontium carbonate
			Bd Wt			2160 (30% decr bd wt gain)	
19	Rat (NS)	>7 mo ad lib (F)	Musc/skel			1570 (rickets: abnormal bone mineralization)	Storey 1962 Strontium carbonate
20	Rat (Sprague-Dawley)	26 d ad lib (F)	Musc/skel			1520 M (rickets)	Svensson et al. 1987 Strontium chloride
			Endocr	1520 M			
			Bd Wt		1520 M (16% decr bd wt gain)		
			Metab	1520 M			
21	Mouse (C57BL/6J)	29 d ad lib (W)	Musc/skel		350 M (11% decr number of osteoclasts; decr bone resorption; 10% incr osteoid surface)		Marie and Hott 1986 Strontium chloride
			Bd Wt	350 M			
			Metab	350 M			

Table 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
22	Rat (Sprague-Dawley)	PND 21-64 (F)				565 M (paralysis of hindlimbs)	Johnson et al. 1968 NS

[a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate oral MRL of 2.0 mg/kg/day. The MRL was derived by dividing the NOAEL by an uncertainty factor of 30(10 for extrapolation from animals to humans, and 3 for human variability), and by a modifying factor of 3(for limited endpoint examination and short duration).

[c] Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Ad lib - ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); decr = decreased; (F) = food; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; hr = hour(s); incr = increased; LD50 = lethal does, 50% kill; LOAEL = lowest-observed-adverse-effect level; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NR = not reported; (NS) = not specified; PND = post natal day; wk = week(s); x = time(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral

Acute (≤14 days)

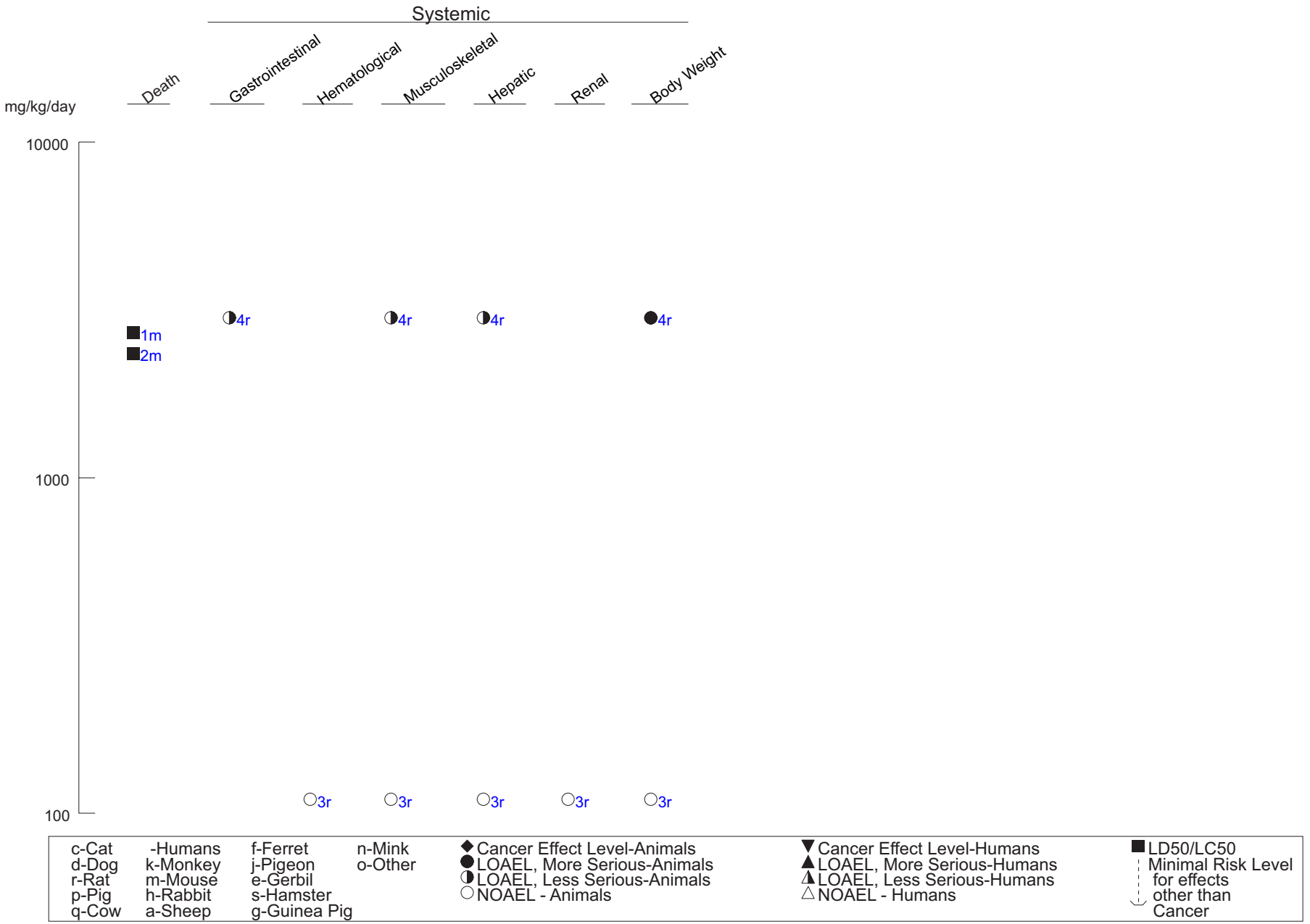


Figure 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

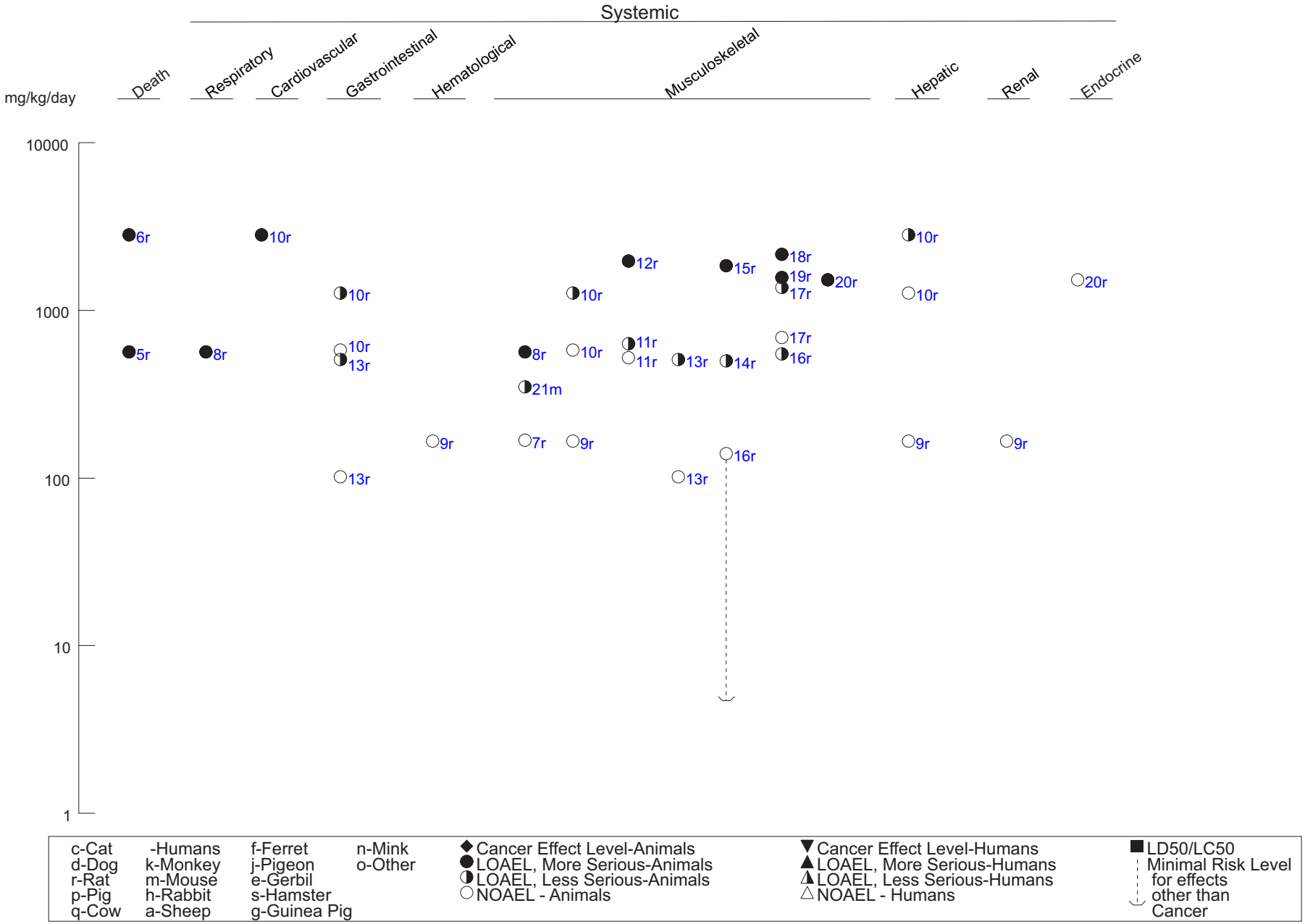
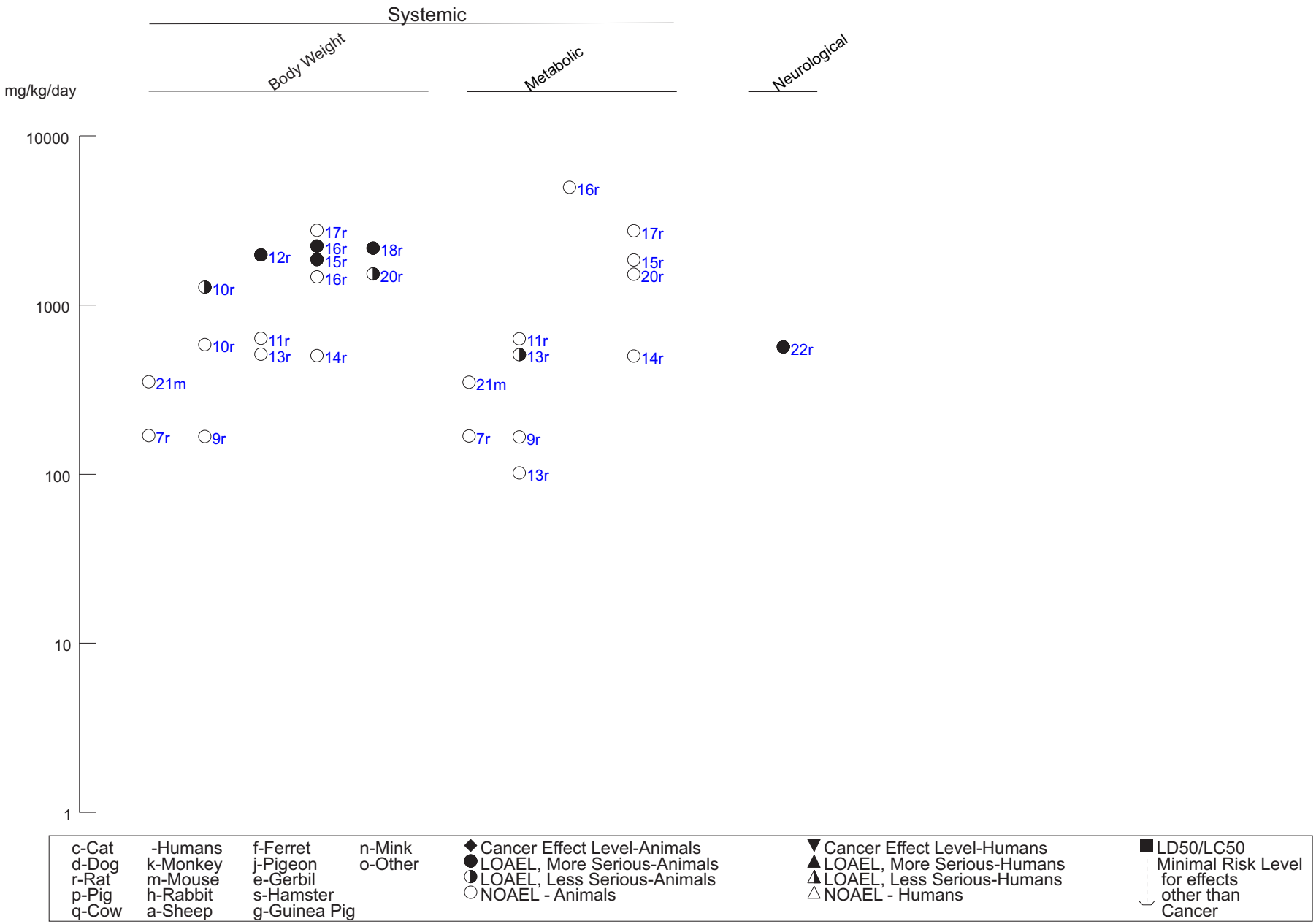


Figure 3-1 Levels of Significant Exposure to Strontium - Chemical Toxicity - Oral (*Continued*)

Intermediate (15-364 days)



(form unspecified) for 4–6 weeks (Johnson et al. 1968). No description of the respiratory effects or incidence data were reported.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following acute- or intermediate-duration oral exposure to stable strontium.

One epidemiological study examined the relationship between trace metals, including strontium, in drinking water and the rates of various kinds of vascular disease in 24 communities in the lowest quartile of the economic scale in Texas (Dawson et al. 1978). The concentration of strontium was measured in samples of drinking water and 2,187 urine samples from subjects (aged 5–97 years) in families that had resided within their respective communities for at least 10 years. There was a significant correlation between mean strontium levels in drinking water and in the urine. However, the only statistically significant product-moment correlationship for strontium (in urine and in drinking water) was for a decreased community mortality rate (in people over 45 years old) for hypertension with heart disease. There was no correlation found between strontium and mortality from arteriosclerotic and degenerative heart disease, other heart diseases, hypertension, general arteriosclerosis, or vascular diseases of the central nervous system.

No studies were located regarding cardiovascular effects after acute- or chronic-duration oral exposure in animals. In male weanling Wistar rats (5–6 per group) given strontium as strontium phosphate in the diet for 4–6 weeks, hemorrhage (unspecified) occurred at 2,820 mg strontium/kg/day, possibly related to the increased mortality at this dose level, but not at or ≤1,270 mg strontium/kg/day (Kshirsagar 1976).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to stable strontium.

No studies were located regarding gastrointestinal effects in animals following chronic-duration oral exposure to various forms of stable strontium. Acute- and intermediate-duration oral studies in animals have examined gastrointestinal effects that would be likely to influence calcium and phosphorus metabolism. Decreases in acid and alkaline phosphatase activities were observed in the small intestine of 5–6 male weanling (21 days old) Wistar rats given 3,000 mg strontium/kg/day as strontium phosphate for 2 weeks (Kshirsagar 1976). These effects were reversed by giving the rats a normal low-strontium diet for 2 weeks. The biological significance of the decreased phosphatase activities is not known. Studies in

chickens first demonstrated the relationship between strontium toxicity, calcium, and vitamin D. In male white Leghorn chickens raised on a diet deficient in vitamin D for the first 2 weeks of life, ingestion of >2,300 mg strontium/kg/day as strontium carbonate in a low-calcium, low-vitamin D diet for 11–14 days, affected calcium transport in the duodenum (Omdahl and DeLuca 1972). Strontium ingestion reduced the duodenal activation of vitamin D_3 (conversion of 25-hydroxycholecalciferol to 1,25-dihydroxy-cholecalciferol), reduced the activity of calcium binding protein, and reduced the absorption of calcium by the duodenum. Similar effects were observed in chickens given excess strontium in a diet with adequate vitamin D, but deficient in calcium (0.01%) (Corradino and Wasserman 1970; Corradino et al. 1971a, 1971b). In addition, excess strontium ingestion significantly reduced the absorption of glucose, histidine, and alanine by the duodenum to levels typical of rachitic (vitamin D-deprived) chickens (Corradino et al. 1971b). The effects of strontium on calcium transport by the duodenum were reversed by transferring chickens to a normal low-strontium diet containing adequate amounts of vitamin D_3 and calcium. The chicken data are not included in Table 3-2, because the physiological rates are likely to be very different from mammals, and also because health risk assessment methodology is currently limited to mammals. However, these phenomena were confirmed in a recent study in rats (Armbrecht et al. 1998). Six days on a diet low in calcium, but containing 0.8% strontium, was sufficient to suppress the serum levels of activated vitamin D, the concentrations of calbindin D protein (two calcium-binding protein induced by vitamin D; see Sections 3.6.1 and 3.6.2), and the rates of calcium transport in the duodenum of young, adult, and old rats.

In male weanling (3 weeks old) Wistar rats (5–6 per group) given strontium phosphate in the diet for 6 weeks, a decrease in alkaline phosphatase activity in the small intestine occurred at 1,270 mg strontium/kg/day, but not at 580 mg strontium/kg/day (Kshirsagar 1976). This decrease in enzyme activity was partly reversed by feeding the rats a normal low-strontium diet for 2 weeks. As mentioned above, the biological significance of these changes in phosphatase activity is not known. In slightly older female juvenile Wistar rats (36 days old, 6–8 per group) that ingested 510 mg strontium/kg/day as strontium carbonate for 27 days, the net intestinal absorption of calcium was reduced by 20%, but no effects occurred at 100 mg strontium/kg/day (Morohashi et al. 1994). In male white Leghorn chickens fed 255 mg strontium/kg/day (probably as carbonate) in a diet low in vitamin D_3 for the first 16 days after hatching, the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol and the transport of calcium were suppressed in the duodenum (Omhdahl and DeLuca 1971). This study is omitted from Table 3-1 because of probable differences in physiology.

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to stable strontium.

No studies were located regarding hematological effects in animals following chronic-duration oral exposure to stable strontium. In adult Wistar rats given up to 110 mg strontium/kg/day as strontium chloride in the diet for 2 weeks, the total number of erythrocytes was slightly elevated in both sexes, and the leucocyte count was slightly elevated in males at the highest dose level at termination (Kroes et al. 1977). However, since the results were not reported quantitatively, the significance of this information is uncertain. No hematological changes were observed among weanling Wistar rats fed up to 166 mg strontium/kg/day as strontium chloride in the diet for 90 days (Kroes et al. 1977). However, the relatively high level of calcium (0.85%) in the diet given to these animals may have reduced absorption and therefore the effect of strontium.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after acute-duration oral exposure to stable strontium. The only long-term human exposure study is an epidemiological study that was carried out in the Ulaş Health Region of Sivas, Turkey (Özgür et al. 1996). This region has a high prevalence of childhood rickets, 32% compared to 4.4% nationally among children aged up to 5 years, and the study sought to determine whether higher levels of strontium in the soil might be a contributing factor. Soils surrounding 55 villages were characterized as to strontium concentration (Group 1, >350 ppm; Group 2, <350 ppm). A total of 2,140 children (ages 6–60 months) from these localities (613 in Group 1 and 1,527 in Group 2) were examined for one or more signs of rickets: craniotabes (localized craniomalacia or thinning of cranium), rachitic rosary (beadlike growths at the ends of ribs where they join cartilage), conspicuous bulging at the wrist, bony deformities of the legs (bowleg, knock-knee), and delayed closure of the fontanelles. A significantly higher proportion of Group 1 children had one or more rachitic signs than those in Group 2: 37.5 vs 19.5%. In addition, the severity of disease (number of rachitic signs per child) was proportionally higher in Group 1 ($p<0.001$). For each cohort, the incidence of rickets was higher in Group 1 than in Group 2 and the differences were statistically significant for ages 6–12, 13–18, 25–36, and 37–48 months (odds ratios 1.66–2.55). When the duration of breast feeding was considered, the incidence of rickets within the two groups did not differ for children breast fed for 24 months or longer. However, for shorter periods of breast feeding, between 0 and 24 months, the incidence of rickets was significantly higher in Group 1 (odds ratios 1.79–3.14). The implication of this study is that breast feeding may be protective against strontium toxicity in nursing infants, probably by providing both calcium and protein, both of which tend to reduce the incorporation of strontium into bone (see Sections 3.10, 3.11, and 3.12.2). The authors attributed the higher incidence of

rickets in Group 1 children to their diet, which, after weaning, is mainly based on grains grown in strontium-rich soil.

No studies were located regarding musculoskeletal effects in animals after chronic-duration oral exposure to stable strontium. Acute- and intermediate-duration studies in animals documented significant adverse effects of strontium on bone that were especially severe in the young. In an acute-duration study, there was no effect on bone in groups of adult SPF Wistar rats that ingested up to 110 mg strontium/kg/day as strontium chloride in the diet for 2 weeks (Kroes et al. 1977). Strontium was detected in bone following ingestion of 11 or 110 mg/kg/day, but not at lower doses (0.1 or 1.0 mg/kg/day). Among male weanling (21 days old) Wistar rats that ingested 3,000 mg strontium/kg/day as strontium phosphate in the diet for 2 weeks, alkaline phosphatase activity was significantly increased in bone compared to controls (Kshirsagar 1976). The author speculated that the observed increase in alkaline phosphatase activity may have been related to a stimulation of osteoblasts, which secrete osteoid and have a high alkaline phosphatase content. In acute studies on young chickens fed 2,300–2,400 mg/kg/day of strontium, and an inadequate level of calcium, severe defects in bone organization and decreased mineralization were observed within 1 or 2 weeks (Corradino and Wasserman 1970; Corradino et al. 1971a, 1971b; Omdahl and DeLuca 1972): abnormally wide hypertrophic cartilaginous zone and impaired endochondral ossification (the removal of hypertrophic cartilage and its replacement by bone). As noted above, the chicken data are omitted from Table 3-1.

Numerous abnormalities of bone structure and bone mineralization were observed in weanling male Sprague-Dawley rats (100–125 g) that ingested 500 mg strontium/kg/day as strontium carbonate in the diet for 3 weeks (Neufeld and Boskey 1994). In strontium-fed rats, the ash weight (mineral content) of metaphyseal bone was reduced and the complexed acidic phospholipid content (lipid nucleator of bone mineral) was significantly higher than in controls. Large areas of nonmineralized bone (osteoid) were observed in epiphyseal bone and secondary spongiosa. The epiphyseal plates were abnormally wide and the metaphyses were abnormally long and dense. The diaphyses contained localized areas of decreased bone density. The primary spongiosa of the proximal tibia was longer and the trabeculae was disorganized and apparently disconnected from the overlying calcified cartilage. The authors suggested that since the levels of complexed acidic phospholipids were high and vitamin D deficiency is known to increase complexed acidic phospholipid levels, that the effect of strontium was probably not mediated through its effect on vitamin D. They suggested the binding of strontium to the surface of initial hydroxyapatite crystallites reduced their further proliferation, resulting in a smaller crystal size.

Similarly, significant abnormalities of bone organization occurred in five weanling (21 days old) male England Wright Y rats that ingested 1,850 mg strontium/kg/day (form unspecified) for 20 days in a diet sufficient in calcium, phosphorus, and vitamin D (Reinholt et al. 1984). In treated rats, the mean thickness of the epiphyseal growth plate was 70% larger than normal. In the epiphyseal regions of long bones, the volume of each zone was larger than its normal counterpart, and in addition, the relative sizes were altered; the proportional volumes of the resting, proliferative, and calcifying zones were significantly smaller and that of the hypertrophic zone was significantly larger than normal. There was an increase in the volume of extracellular matrix in bone, suggested to be associated with a reduced rate of extracellular matrix vesicle degradation. Another study from this laboratory examined the biochemistry of epiphyseal cartilage in rats treated as above (Reinholt et al. 1985). In strontium-treated rats, alterations were observed in the proteoglycan composition (slightly higher galactosamine content), chondroitin sulfate chain lengths (larger), regional distributions of large and small chondroitin sulfate peptides, and regional distributions of both non-sulfated chondroitin sulfate disaccharides and hyaluronic acid-disaccharides. The authors suggested that these strontium-induced alterations in cartilage matrix might affect the process of mineralization.

No effects on bone histology were observed in young female rats (40–60 g) that were fed 140 mg strontium/kg/day as strontium carbonate for 20 days, but histological abnormalities were detected at doses between 550 and 4,975 mg/kg/day (Storey 1961). Alterations in the appearance of the cartilage plate (irregular, thicker, with areas of uncalcified bone matrix in the distal ends of the metaphyseal trabeculae and proximal end of the diaphysis) were observed at 550 mg strontium/kg/day. Irregularities in the organization of the cells of hypertrophic zone (distorting the usual parallel arrangement of intercellular matrix columns), in the pattern of calcification, and in deposition of osteoid were more conspicuous with increasing dose. At higher doses, bands of uncalcified cartilage matrix were isolated between areas of osteoid tissue. In tibias, the dry weight, ash weight, ash percentage, and calcium in ash were significantly reduced with increased strontium intake. In the same study, adult female rats given doses of 170–2,750 mg strontium/kg/day exhibited milder effects in bone. Histological changes in the tibia (thicker epiphyseal cartilage, increased width of metaphyseal osteoid seams) were noted at 1,370 or 2,750 mg strontium/kg/day only. Other significant effects seen only at 2,750 mg strontium/kg/day included the deposition of osteoid tissue near vascular canals, a reduction in the area of bone resorption, and reductions in the dry weight, ash weight, ash percentage, and calcium in ash of bone (Storey 1961).

A 24% reduction in bone formation rate, 28% reduction in bone resorption rate (based on ^{45}Ca uptake), and a significantly reduced calcium content in ashed femurs, but no change in ash weight were observed

after female juvenile Wistar rats (36 days old) ingested 510 mg strontium/kg/day as strontium carbonate in the diet for 27 days (Morohashi et al. 1994). These rats were also significantly hypocalcemic. No effects were observed at 50 or 100 mg strontium/kg/day other than an unexplained increase in calcium content of bone at 50 mg strontium/kg/day (Morohashi et al. 1994). Minor bone effects occurred in 21-day-old male C57BL/6J mice after ingesting 350 mg strontium/kg/day as strontium chloride in the drinking water for 29 days (Marie and Hott 1986). Strontium had no significant effect on tibial length or bone mineral content (percent ash, calcium, or phosphorus). In vertebrae, strontium had no effect on the osteoblastic surface (percent endosteal surface showing plump osteoblasts), bone matrix apposition rate, osteoid seam thickness (average width of all endosteal osteoid seams), or calcified bone volume. However, exposure to strontium resulted in a 10% increase in osteoid surface (percent endosteal surface covered by an osteoid seam) and an 11% reduction in the number of active osteoclasts.

There was radiographic evidence of abnormally thickened epiphyseal cartilage plates in the long bones of weanling male Wistar rats exposed to strontium phosphate in the diet at a dose level of 2,820 mg strontium/kg/day for 4–6 weeks, but no effect at 580 mg strontium/kg/day and little effect at 1,270 mg strontium/kg/day (Kshirsagar 1976). Ingestion of 565 mg strontium/kg/day for 43 days resulted in several bone abnormalities in young Sprague-Dawley rats (Johnson et al. 1968). The level of sodium in bone was significantly lowered, and the level of potassium was significantly increased, and the overall index of bone mineralization (percent bone ash) was decreased. Unmineralized osteoid was visible in histological sections of vertebrae. Rats became rachitic and osteomalacic and exhibited paralysis of the hindlimbs.

Beneficial effects of a low dose of strontium were noted on bone mineralization, such as a 17% increase in mineral bone volume and a 70% increase in the number of bone forming sites, with no adverse effect on the hydroxyapatite mineral particle size in 28-day-old male Sprague-Dawley rats ingesting 168 mg strontium/kg/day in an unspecified form for 8 weeks (Grynpas et al. 1996) or in young SPF Wistar rats fed doses up to 166 mg strontium/kg/day as strontium chloride in the diet for 90 days (Kroes et al. 1977). Stimulation of calcified bone growth was noted among male weanling Sprague-Dawley rats ingesting between 316 and 524 mg strontium/kg/day as strontium chloride for 9 weeks, but reduced bone calcification was observed at 633 mg/kg/day (Marie et al. 1985). In male weanling Sprague-Dawley rats ingesting 1,520 mg strontium/kg/day for 26 days, epiphyseal growth plates had abnormally thick hypertrophic zones and impaired calcification and resorption at the metaphyseal side (Svensson et al. 1985, 1987). In addition, cartilage from strontium-treated rats contained 75% less calcium and had a 60% lower rate of synthesis of glycosaminoglycans and collagen. When 4-week-old male Wistar rats (50–60 kg body weight) were fed 1,970 mg strontium/kg/day as strontium carbonate in a diet low in calcium

(0.04%), bone mineralization was significantly affected (Matsumoto 1976). This study is presented in detail in Section 3.2.2.6 Developmental Effects, as an example of skeletal anomalies in young animals resulting from strontium ingestion.

In another intermediate-duration animal study, young (50–70 g) rats ingested 2,160 mg strontium/kg/day and adult rats ingested 1,570 mg strontium/kg/day as strontium carbonate for 7 months (Storey 1962). At 3 weeks, young rats developed a rachitic gait, and subsequently, some rats (numbers not specified) developed spinal kyphosis, bent tibiae, and irregular discolored enamel on anterior teeth. Histological abnormalities in long bone differentiation included reduced calcification, excess growth of epiphyseal cartilage, abnormal deposition of osteoid (unmineralized bone) in the metaphysis, fragmentation of the epiphyseal plates, and isolated nodules of cartilage. Osteoid accumulation was observed in the skull. Adult rats were affected by strontium ingestion in the same way, but to a lesser degree than young animals. Abnormal depositions of osteoid in long bones and skull were not as extensive as in young rats. The epiphyseal plate did not become fragmented. Tooth enamel was abnormally white and pitted.

Hepatic Effects. No studies were located regarding hepatic effects in humans following oral exposure to stable strontium.

No studies were located regarding hepatic effects in animals after chronic-duration oral exposure to stable strontium. In acute- and intermediate-duration studies, in which the diet contained adequate amounts of calcium and vitamin D, few hepatic effects were reported. No histological changes were observed in the livers of adult Wistar rats given up to 110 mg strontium/kg/day as strontium chloride in the diet for 2 weeks (Kroes et al. 1977). Acid phosphatase activity decreased by about 8% in the livers of 5–6 male weanling (21 days old) Wistar rats given 3,000 mg strontium/kg/day as strontium phosphate for 2 weeks (Kshirsagar 1976). However, this effect was reversible by feeding the rats a normal, low-strontium diet for 2 weeks. In male weanling Wistar rats, ingestion of strontium phosphate in the diet for 4–6 weeks resulted in a >26% decrease in hepatic alkaline phosphatase activity at 2,820 mg strontium/kg/day, but no decrease at 1,270 mg strontium/kg/day (Kshirsagar 1976). The biological significance of these small, but statistically significant, changes in hepatic phosphatase activity is not known. Among weanling male and female Wistar rats fed strontium chloride in the diet for 90 days, the only hepatic effects were ‘slight histological changes’ (not described) and an ‘increase in peripheral glycogen’ in females at the highest dose (166 mg strontium/kg/day); no other hepatic effects were observed in either sex ≤146 mg strontium/kg/day (Kroes et al. 1977).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to stable strontium.

No studies were located regarding renal effects in animals after chronic-duration oral exposure to stable strontium. In acute- and intermediate-duration studies, in which the diet contained adequate amounts of calcium and vitamin D, no renal effects were reported. No organ weight or histological changes were observed in the kidneys of adult Wistar rats given up to 110 mg strontium/kg/day as strontium chloride in the diet for 2 weeks (Kroes et al. 1977). Similarly, no such changes were observed among weanling Wistar rats fed up to 166 mg strontium/kg/day as strontium chloride in the diet for 90 days (Kroes et al. 1977). In male white Leghorn chickens raised on a diet deficient in vitamin D for the first 2 weeks of life, ingestion of 2,350 mg strontium/kg/day in a low-calcium, low-vitamin D diet for 7 additional days, reduced the activation of vitamin D_3 in mitochondria of the kidney (Omdahl and DeLuca 1972). Because of physiological differences between birds and mammals, this study is omitted from Table 3-1.

Endocrine Effects. Few studies were located regarding endocrine effects in humans after oral exposure to stable strontium. Vezzoli et al. (1998) reported that strontium absorption was inversely correlated with parathyroid hormone levels.

No studies were located regarding endocrine effects in animals of acute- or chronic-duration oral exposure to stable forms of strontium. There were no histological changes in the parathyroid gland or alterations in parathyroid hormone levels observed in male weanling Sprague-Dawley rats given 1,520 mg strontium/kg/day in the diet for 26 days (Svensson et al. 1987). The authors cautioned that their biochemical methods could not distinguish between active and inactive forms of the hormone. A few organ weight changes were observed among weanling Wistar rats fed up to 166 mg strontium/kg/day as strontium chloride in the diet for 90 days (Kroes et al. 1977). The relative thyroid weight was significantly heavier in males at 36 and 146 mg strontium/kg/day and the relative pituitary weight was significantly decreased in females at 10 and 166 mg strontium/kg/day, but in neither case was there a clear dose-response. Slight histological changes in the thyroid were reported.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to stable strontium.

No studies were located regarding body weight effects in animals after chronic-duration oral exposure to stable strontium. In acute- and intermediate-duration animal studies, the effective dose levels for body

weight effects were relatively high and young animals were more sensitive than adults. In an acute-duration study, there was no effect on body weight in groups of adult SPF Wistar rats that ingested up to 110 mg strontium/kg/day as strontium chloride in the diet for 2 weeks (Kroes et al. 1977). Body weight gain was reduced by 62% among male weanling (21-day-old) Wistar rats that ingested 2,820 mg strontium/kg/day as strontium phosphate in the diet for 2 weeks, but this effect was reversible by feeding rats a diet low in strontium for 2 weeks (Kshirsagar 1976). From an analysis of a pair-fed control group (food intake matched to this high-dose group), the author concluded that the severe effects were a result of excess strontium, and not the reduced diet. Ingestion of 1,090 or 1,630 mg strontium/kg/day as strontium lactate reduced body weight gain in 5-week-old albino rats within several days (Teree et al. 1965). However, it seems likely that the reduced body weight gains resulted from an observed (but not measured) reduction in food intake, possibly because of reduced palatibility at the higher dose levels. Since the reduction appears not to be a systemic effect of strontium ingestion, this study is omitted from Table 3-1.

Most of the intermediate-duration oral exposure studies in weanling rodents have reported no effect on body weight for exposures <633 mg strontium/kg/day (rats: Grynpas et al. 1996; Kroes et al. 1977; Marie et al. 1985; Morohashi et al. 1994; Neufeld and Boskey 1994; Skoryna 1981a; and mice: Marie and Hott 1986). Intermediate-duration exposures to stable strontium at levels above 1,000 mg/kg/day adversely affected body weight. A 15% reduction in body weight gain was observed among weanling (21-day-old) male Wistar rats that ingested 1,270 mg strontium/kg/day as strontium phosphate for 4–6 weeks, but no reduction was observed at 580 mg strontium/kg/day (Kshirsagar 1976). The body weight gain was 28% lower than controls in weanling (21-day-old) male England Wright Y rats that ingested 1,850 mg strontium/kg/day (form unspecified) for 20 days (Reinholt et al. 1985). The terminal body weight was 16% lower than normal in male weanling Sprague-Dawley rats that ingested 1,520 mg strontium/kg/day (form not specified in this paper, but other publications from this lab used strontium chloride) for 26 days (Svensson et al. 1987).

A >30% loss in body weight occurred in young female rats (40–60 g) that were fed 4,975 mg strontium/kg/day as strontium carbonate for 20 days (Storey 1961); body weight gain was reduced by 24% at 2,220 mg, but was unaffected at 1,460 mg strontium/kg/day. Food intake was not reported, so it is uncertain to what extent these results are attributable to unpalatability. Similarly treated adult female rats exhibited no significant body weight changes at 2,750 mg strontium/kg/day (Storey 1961). Body weight gain was about a third lower than controls in young (50–70 g) rats that ingested 2,160 mg

strontium/kg/day as strontium carbonate for 7 months (Storey 1962); no quantitative body weight data were reported for young or adult animals.

In acute- and intermediate-duration studies, strontium effects on body weight were more severe in animals on diets low in calcium. Reduced body weight gain was reported in young white Leghorn chicks following ingestion of a high strontium/low calcium diet for 1 or 2 weeks (Corradino and Wasserman 1970; Corradino et al. 1971a, 1971b). The body weight gain of male weanling Wistar rats was reduced by 60% after ingestion of strontium carbonate (1,960 mg strontium/kg/day) in a diet low in calcium (0.04%) for 4 weeks (Matsumoto 1976).

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to stable strontium.

No studies were located regarding metabolic effects in animals after chronic-duration oral exposure to stable strontium. In animal studies, few metabolic effects resulted from acute- or intermediate-duration oral exposure to stable strontium. In chicks given a normal Vitamin D_3-containing diet for 2 weeks after hatching, ingestion of a diet containing excess strontium reduced the plasma concentration of calcium, probably a consequence of reduced calcium absorption by the duodenum (Corradino et al. 1971a). Intermediate-duration exposures to 150–1,850 mg strontium/kg/day as strontium carbonate or strontium chloride had no effects on the serum levels of calcium, phosphorus, or magnesium in young or adult rodents given adequate dietary calcium, phosphorus, and vitamin D (rats: Grynpas et al. 1996; Kroes et al. 1977; Marie et al. 1985; Neufeld and Boskey 1994; Svensson et al. 1985, 1987; Reinholt et al. 1984; Skoryna 1981a; and mice: Marie and Hott 1986). No effects on serum calcium levels were observed in young female rats (40–60 g) that were fed 4,975 mg strontium/kg/day as strontium carbonate for 20 days or in adult female rats similarly fed 2,750 mg strontium/kg/day (Storey 1961). At 4,975 mg strontium/kg/day in the young rats, the calcium/strontium ratio was 1, whereas the ratio at 2,750 mg strontium/kg/day in adult rats was 1.4. A 13% reduction in serum calcium was observed in female juvenile Wistar rats (36-day-old, 6–8 per group) that ingested 510 mg strontium/kg/day as strontium carbonate in the diet for 27 days, but no effect was observed at 100 mg strontium/kg/day (Morohashi et al. 1994).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located that reported immunological or lymphoreticular effects in humans or animals following oral exposure to stable strontium.

3.2.2.4 Neurological Effects

No studies were located that reported neurological effects in humans following oral exposure to stable strontium. No behavioral effects were observed in rats that ingested strontium chloride at levels up to 110 mg strontium/kg/day for 2 weeks or 166 mg strontium/kg/day for 90 days (Kroes et al. 1977). Johnson et al. (1968) reported paralysis of the hindlimbs in weanling male Sprague-Dawley rats that were fed 565 mg/kg/day of stable strontium (form not specified) for 43 days. It is not clear whether the observed paralysis was neurological or muscular, but it could have been related to abnormal calcium signaling in muscle or nerve. It is unlikely that the paralysis was due to the deformation of the femora as severely rachitic and osteomalacic rodents are not generally paralyzed. The NOAEL and LOAEL are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following oral exposure to stable strontium.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following acute- or intermediate-duration oral exposure to stable forms of strontium. The only chronic-duration study is the Turkish epidemiological analysis that found a relationship between the concentration of strontium in the local soil and the prevalence of rickets in children between the ages of 6 months and 5 years (Ögzur et al. 1996). A relatively short period of breast feeding, which presumably affected calcium intake, and soil levels of strontium higher than 350 ppm, which probably determined the level of strontium in dietary grains consumed after weaning, were associated with an increase in the prevalence and severity of rickets. This study is discussed above in Section 3.2.2.2 Musculoskeletal Effects.

No studies were located that examined the effect of exposure to stable strontium *in utero* following oral maternal exposure in animals. However, the studies discussed in Section 3.2.2.2 Musculoskeletal Effects address the effects of strontium on bone organogenesis, in particular, endochondral ossification, a developmental process that continues long after birth. For example, in a study in which 4-week-old male Wistar rats (50–60 g body weight) were fed 1,970 mg strontium/kg/day as strontium carbonate in a diet low in calcium (0.04%), bone mineralization was significantly affected (Matsumoto 1976). Tibial length was reduced by 33% and the tibial proximal and distal epiphyseal plates were both about 5 times wider than normal. Microradiographic and histological analyses of tibial proximal heads revealed that no mineralization was detectable, that the organization of chondroblasts was irregular, and that osteoid rather than mineralized bone was deposited. Other studies on weanlings were conducted for acute durations (rat: Kshirsagar 1976) and intermediate durations (rat: Grynpas et al. 1996; Kroes et al. 1977; Morohashi et al. 1994; Neufeld and Boskey 1994; Reinholt et al. 1984, 1985; Svensson et al. 1985, 1987; and mice: Marie and Hott 1986). Intermediate-duration studies on rats demonstrated that ingestion of strontium resulted in more severe skeletal effects in young animals than in adults (Storey 1961, 1962). These studies are described in Section 3.2.2.2 Musculoskeletal Effects and are listed in Table 3-1 and Figure 3-1 under that category.

3.2.2.7 Cancer

No studies were located that demonstrated cancer effects of stable strontium following oral exposure in humans or animals. In one case-control study, no association was found between the incidence of liver cancer in 1984 on Chongming Island in China and the levels of stable strontium detected in hair (Wang et al. 1990).

3.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to stable strontium:

3.2.3.1 Death

3.2.3.2 Systemic Effects

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

This section includes injection and *in vitro* studies that provide evidence for the biological basis of toxicity of stable strontium in humans and animals. Since these studies are not directly relevant to general population exposure conditions, no LSE tables have been created for this section.

Cardiovascular Effects. Cardiovascular effects of strontium have been investigated by intravenous infusion studies in dogs. Infusions of strontium (as chloride or gluconate) averaging 172 mg strontium/kg under conditions of lowered potassium induced accelerated ventricular escape beats, ventricular tachycardia, or atrial fibrillation (Foster et al. 1977). High levels of strontium also induced oscillatory potentials and prolonged depolarization (precursors to arrhythmia) in Purkinje fibers of isolated sheep hearts (Gonzalez and Vassalle 1990). Whereas intravenous infusions at 4 mg strontium/kg had no effect on cardiac physiology, infusions at ~15 mg strontium/kg that brought the strontium/Ca ratio above 1 had a temporary negative chronotropic effect, reduced cardiac output, increased pulmonary vascular resistance, and systemic vascular resistance, but had no effect on pulmonary or systemic arterial pressure or pulmonary wedge pressure (Barry et al. 1972; Skoryna et al. 1986). The concentrations of strontium used in these studies are very high relative to the mean concentration of strontium in human blood, 27 µg strontium/L (see Table 6-9).

Hematological Effects. Because of its molecular similarity to calcium, the association of stable strontium with several kinds of blood cells has been investigated in a number of *in vitro* experiments. Strontium ions were found to be transported across the cell membrane of human erythrocytes by means of an ATP-dependent calcium pump (de la Sierra et al. 1990; Olson 1979; Olson and Cazort 1969; Porzig 1973). In washed platelets from human and rabbit, strontium stimulated the secretion of

5-hydroxytryptamine (Best et al. 1981; Bone et al. 1980; Togna et al. 1989). Best et al. (1981) concluded that strontium activates the release of arachidonate from platelet membrane phospholipid, with the subsequent synthesis of thromboxane A_2, a reaction that was antagonized by aspirin. These authors also suggested that strontium, because of its smaller hydrated ionic radius compared to calcium, is able to enter the platelet and mimic the rise in cytosolic calcium concentration that normally serves to activate secretion of 5-hydroxytryptamine (Best et al. 1981). Strontium was also found to stimulate degranulation of human large granular lymphocytes, which resulted in the inhibition of natural killer (NK) cells (Neighbour et al. 1982). The content of strontium (and calcium) was found to be significantly elevated above healthy control levels in granulocytes isolated from Swedish patients with active rheumatoid arthritis or seronegative spondarthritis (Hällgren et al. 1984). The strontium overload was thought to be linked to the degree of inflammation, and was positively related to serum levels of the acute-phase protein haptoglobin; corticosteroid therapy differentially reduced the strontium content of granulocytes compared to calcium. The authors suggested that leukocyte endogenous mediator (LEM) regulated the accumulation of strontium in granulocytes.

Immunological and Lymphoreticular Effects. Several *in vitro* experiments have demonstrated that strontium, although less efficient than calcium, is able to stimulate histamine release from rat mast cells (Alm and Bloom 1981a, 1981b; Atkinson et al. 1979; Foreman 1977; Foreman and Mongar 1972a, 1972b; Foreman et al. 1977). This is probably relevant to humans, since strontium has been shown to degranulate human lymphocytes (Neighbor et al. 1982) and stimulate the release of 5-hydroxytryptamine by human platelets (Best et al. 1981) (see Hematological Effects above). In rabbit blood treated with strontium chloride in vitro, the bacterocidal properties of serum were reduced (Toshioka et al. 1974); this effect was attributed to the inhibition of complement.

Neurological Effects. *In vitro* studies have demonstrated subtle differences between strontium and calcium with respect to neurological function at the cellular level. In a calcium-free medium, strontium ion weakly supported the generation of excitatory postsynaptic potentials following stimulation of guinea pig superior cervical ganglia (i.e., the release of acetylcholine was less efficient than when calcium was present) (McLachlan 1977). Calcium is sequestered in mitochondria and smooth endoplasmic reticulum of isolated presynaptic nerve terminals in preference to strontium (Rasgado-Flores et al. 1987). Strontium ion inhibits the uptake of calcium by synaptic vesicles in vitro, thereby blocking the antiport-regulated release of H+ (Gonçalves et al. 1999). Strontium ion was slightly more efficient than calcium ion in supporting the release of neurotransmitter from synaptosomes induced by leptinotoxin-h (Madeddu et al. 1985). Strontium ion was found to support the asynchronous mode of transmitter release in isolated layer

V pyramidal cells of the prefrontal cortex (Aghajanian and Marek 1999). This is apparently mediated through calcium-binding protein synaptotagmin III, as strontium does not support the function of calcium-binding synaptotagmins I and II (Li et al. 1995).

Reproductive Effects. The results of one *in vitro* study suggest that stable strontium is not directly harmful to human spermatozoa. In developing an improved method to be used by fertility clinics for testing the functional capacity of human spermatozoa, it was found that inclusion of strontium chloride in the testing medium improved the rate of penetration compared to calcium chloride (Mortimer 1986; Mortimer et al. 1986).

Developmental Effects. Subcutaneous injection of up to 82 mg strontium/kg/day as strontium nitrate into female Wistar rats between days 9 and 19 of gestation had no teratogenic effect, no adverse effect on the ossification of the skeleton, and no effect on the number of resorptions (Lansdown et al. 1972).

3.3 DISCUSSION OF HEALTH EFFECTS OF RADIOACTIVE STRONTIUM BY ROUTE OF EXPOSURE

Section 3.3 discusses radiation toxicity associated with exposure to radionuclides of strontium and is organized in the same manner as that of Section 3.2, first by route of exposure (inhalation, oral, and external) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing NOAELs or LOAELs reflect the actual dose (levels of exposure) used in the studies. Refer to Section 3.2 for detailed discussion of the classification of endpoints as a NOAEL, less serious LOAEL, or serious LOAEL.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of radiostrontium are indicated in Tables 3-2, 3-3, and 3-4 and Figures 3-2 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-2 and 3-3 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Refer to Appendix B for a User's Guide, which should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

3.3.1 Inhalation Exposure

The two major sources of data regarding health effects of inhaled radioactive strontium are long-term studies using beagles at the Lovelace Foundation, Albuquerque, New Mexico (now known as the Lovelace Respiratory Research Institute). One study examined the acute inhalation effects of a relatively soluble aerosol of $^{90}SrCl_2$, and the other examined the acute inhalation effects of relatively insoluble particles of ^{90}Sr fused to aluminum silicate ('^{90}Sr fused-clay particles').

In the soluble aerosol study, beagles were exposed by nose breathing for varying exposure durations (2–22 minutes) to graded concentrations (2.16–419 μCi ^{90}Sr/L; 0.08–15.5 MBq/L) of $^{90}SrCl_2$ to produce graded levels of initial body burdens. Individual variations in the degree to which aerosol was cleared from the respiratory tract and swallowed contributed to variability in the initial rapid rate of clearance during the first few days. Therefore, exposures were expressed in terms of the long-term retained burden (LTRB), which ranged from 1.08 to 119 μCi (0.04–4.4 MBq) ^{90}Sr/kg of body weight. Radiostrontium quickly passed through the lungs and was overwhelmingly retained in the skeleton, where initial skeletal dose rates were calculated to be 0.43–55 rad/day (0.0043–0.55 Gy/day). Clearance of radiostrontium from the skeleton was gradual. For that reason, the initial and long-term health effects were primarily related to hemopoietic bone marrow and osteogenic tissues. Reports relating to the $^{90}SrCl_2$ aerosol study include Benjamin et al. (1974b, 1975, 1976a, 1976c, 1979), Boecker et al. (1969, 1991), Fission Product Inhalation Project (1967a), Gillett et al. (1987a, 1987b), Hahn et al. (1991), McClellan et al. (1973, 1983a), and Muggenburg et al. (1977, 1978, 1979).

In the other study, beagles were exposed by nose-only inhalation to ^{90}Sr fused-clay particles for initial lung burdens ranging from 0.21 to 94 μCi ^{90}Sr/kg (0.008–3.5 MBq/kg) of body weight. Control animals were exposed to similar aluminosilicate clay particles fused to stable strontium. Early and late-occurring health effects of inhaled particulate radiostrontium were primarily associated with the lung. Some particles were cleared into the lung-associated lymph nodes, where radiation damage led to their entry into the circulatory system, leading to distribution to spleen, liver, and possibly other tissues. Trapping of radioactive particles by these tissues created possible sites for radiation damage and tumor development. The biological retention half-time for ^{90}Sr in fused-clay particles was approximately 490 (±320 days standard deviation). Reports relating to ^{90}Sr fused clay particles include Benjamin et al. (1974a, 1975),

Griffith et al. (1992), Hahn et al. (1983a), Hobbs et al. (1972), Jones et al. (1972, 1976), Scott (1980), and Snipes et al. (1974a, 1974b, 1976, 1977, 1978, 1979). A similar study with a smaller group of dogs was carried out by Benjamin et al. (1976c).

3.3.1.1 Death

No studies were located regarding death in humans following inhalation exposure to radioactive strontium. Information on the lethality of inhaled radioactive strontium is limited to acute exposure studies. Because of the bone-seeking behavior of strontium, an acute exposure to airborne ^{90}Sr results in chronic exposure to radiation from ^{90}Sr incorporated into bone. If insoluble radiostrontium compounds are inhaled, there could be long-term lung exposure (see discussion of the study by Willard and Snyder (1966) in Section 3.5.1.1).

In two different experiments briefly described in a report by the Lovelace Foundation (now known as the Lovelace Respiratory Research Institute), young male and female Holtzman rats were exposed once to ^{90}Sr by whole body inhalation for initial body burdens ranging from 170 to 1,660 μCi ^{90}Sr/kg (0.63–61.4 MBq/kg) of body weight and average skeletal radiation doses ranging from 12,600 to 19,000 rad (126–190 Gy) (Fission Product Inhalation Project 1967b). Survival was inversely proportional to dose, with rats receiving the lowest dose living for more than 700 days, and those receiving the highest dose living less than 200 days. In the two experiments, 77% of the rats that died and 47% of the rats that were killed in a moribund state were found to have osteosarcoma. Among rats dying with tumors, the average skeletal dose was 81 rad/day, compared to 62 rad/day for rats without tumors (0.81 vs 0.62 Gy/day). The small sample sizes in this study do not permit its inclusion in the LSE Table 3-2.

In acute inhalation studies in beagle dogs, high-dose radiation effects of inhaled $^{90}SrCl_2$ on bone marrow resulted in death within days or weeks of exposure, whereas lower doses reduced long-term survival through carcinogenetic effects. For all exposed dogs, the mean survival time was 3,000 days, compared to 4,500 days for the controls (Gillett et al. 1987b). Among dogs receiving high or medium doses (long-term retained body burdens between 47 and 120 μCi ^{90}Sr/kg (1.74 and 4.44 MBq/kg), 6/22 died within 32 days from severe hypoplasia of the bone marrow (Gillett et al. 1987a; Muggenburg et al. 1979). Individual neutrophil counts were the most reliable predictors of lethality. Death from primary bone tumors occurred from 2 to 10 years after exposure to inhaled $^{90}SrCl_2$ (Gillett et al. 1987b). Fibrosarcomas and metastasizing hemangiosarcomas occurred somewhat earlier than osteosarcomas and were the major

contributors to shortened mean survival times for the dogs exposed to inhaled $^{90}SrCl_2$ (Gillett et al. 1987b). Deaths from myelomonocytic leukemia and from bone-associated soft tissues of the skull were also concluded to be associated with radiostrontium; the long-term retained burdens were 9.2–27 μCi ^{90}Sr/kg (0.34–1.0 MBq/kg) and 21–35 μCi ^{90}Sr/kg (0.081–1.3 MBq/kg), respectively. These are extreme doses.

In beagle dogs exposed by acute inhalation to ^{90}Sr fused-clay particles, the pattern of mortality was different since the radioactive particles were initially embedded in the lung. No deaths occurred until the 5th month postexposure. Of 36 dogs with initial lung burdens ≥25 μCi ^{90}Sr/kg (925 kBq/kg) of body weight, 35 died within the first 2 years, primarily of radiation pneumonitis and/or pulmonary fibrosis (Snipes et al. 1979). Subsequently, within the 2nd to 7th years after exposure, deaths from hemangiosarcoma and carcinoma of the lung were common. None of the control dogs died during the 9 years following exposure (Snipes et al. 1979), indicating that the observed mortality was not caused by inhalation of nonradioactive aluminum silicate particles alone. Among dogs dying prematurely from neoplasms of the lung, the initial lung burdens were between 3.7 and 94 μCi/kg (0.14–3.5 MBq/kg) and the doses to the lungs ranged from 43,000 to 67,000 rad (430–670 Gy) (Benjamin et al. 1975).

The percent mortality values for dogs from exposure to radioactive strontium by the inhalation route are presented in Table 3-2 and plotted in Figure 3-2.

3.3.1.2 Systemic Effects

No studies were located that described endocrine, dermal, or ocular effects in humans or animals following inhalation exposure to radioactive strontium. The highest NOAEL values and all reliable LOAEL values in each species and duration category for systemic effects from radiation exposure to strontium by the inhalation route are presented in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. The only respiratory effects reported for the study in which beagle dogs were exposed to soluble aerosols of $^{90}SrCl_2$ (Boecker et al. 1969; Gillett et al. 1987b) were late primary cancers of the respiratory tract or tumors metastasizing to the lung. These effects are discussed in Section 3.2.1.7 Cancer.

Table 3-2 Levels of Significant Exposure to Strontium - Radiation Toxicity - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (µCi/kg)	LOAEL Less Serious (µCi/kg)	LOAEL Serious (µCi/kg)		Reference Chemical Form
	ACUTE EXPOSURE							
	Death							
1	Dog (Beagle)	2-22 min once				47	[LTRB] (6/24 died from bone marrow hypoplasia)	Gillett et al. 1987a Strontium-90 (chloride)
	Systemic							
2	Dog (Beagle)	once	Cardio			25	[ILB] (damaged pulmonary vasculature; hypertrophic right ventricle; congestive heart failure)	Benjamin et al. 1976c Sr-90 (fused-clay particles)
			Hepatic			25	[ILB] (all with chronic passive congestion; one with mild centrilobular fibrosis)	
			Bd Wt			25	[ILB] (emaciation)	
3	Dog (Beagle)	2-22 min once	Gastro			47	[LTRB] (anorexia, bloody diarrhea from acute radiation syndrome)	Gillett et al. 1987a Strontium-90 (chloride)
			Hemato			1.5	[LTRB] (60% decr platelet count)	
			Renal			47	[LTRB] (incr blood urea nitrogen, decr urine output from acute radiation syndrome)	

Table 3-2 Levels of Significant Exposure to Strontium - Radiation Toxicity - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (µCi/kg)	LOAEL Less Serious (µCi/kg)	LOAEL Serious (µCi/kg)		Reference Chemical Form
4	Dog (Beagle)	2-22 min once	Gastro			1.9	[LTRB] (malabsorption syndrome at age >11 yrs)	Muggenburg et al. 1977 Strontium-90 (chloride)
			Bd Wt			1.9	[LTRB] (decr bd wt)	
5	Dog (Beagle)	once	Resp			25	[ILB] (pulmonary pneumonitis, fibrosis)	Snipes et al. 1979 Sr-90 (fused-clay particles)
			Gastro			4.1	[ILB] (ulcerating lesion of pharynx; anorexia)	
	Immuno/ Lymphoret							
6	Dog (Beagle)	once				25	[ILB] (50% decr lymphocytes for 28 weeks)	Benjamin et al. 1976c Sr-90 (fused-clay particles)
7	Dog (Beagle)	2-22 min once				10	[LTRB] (22% decr lymphocyte count lasting 3 years)	Gillett et al. 1987a Strontium-90 (chloride)
8	Dog (Beagle)	once				5	[ILB] (lymphocyte counts decr 40% for two years)	Jones et al. 1976 Sr-90 (fused-clay particles)

Table 3-2 Levels of Significant Exposure to Strontium - Radiation Toxicity - Inhalation (continued)

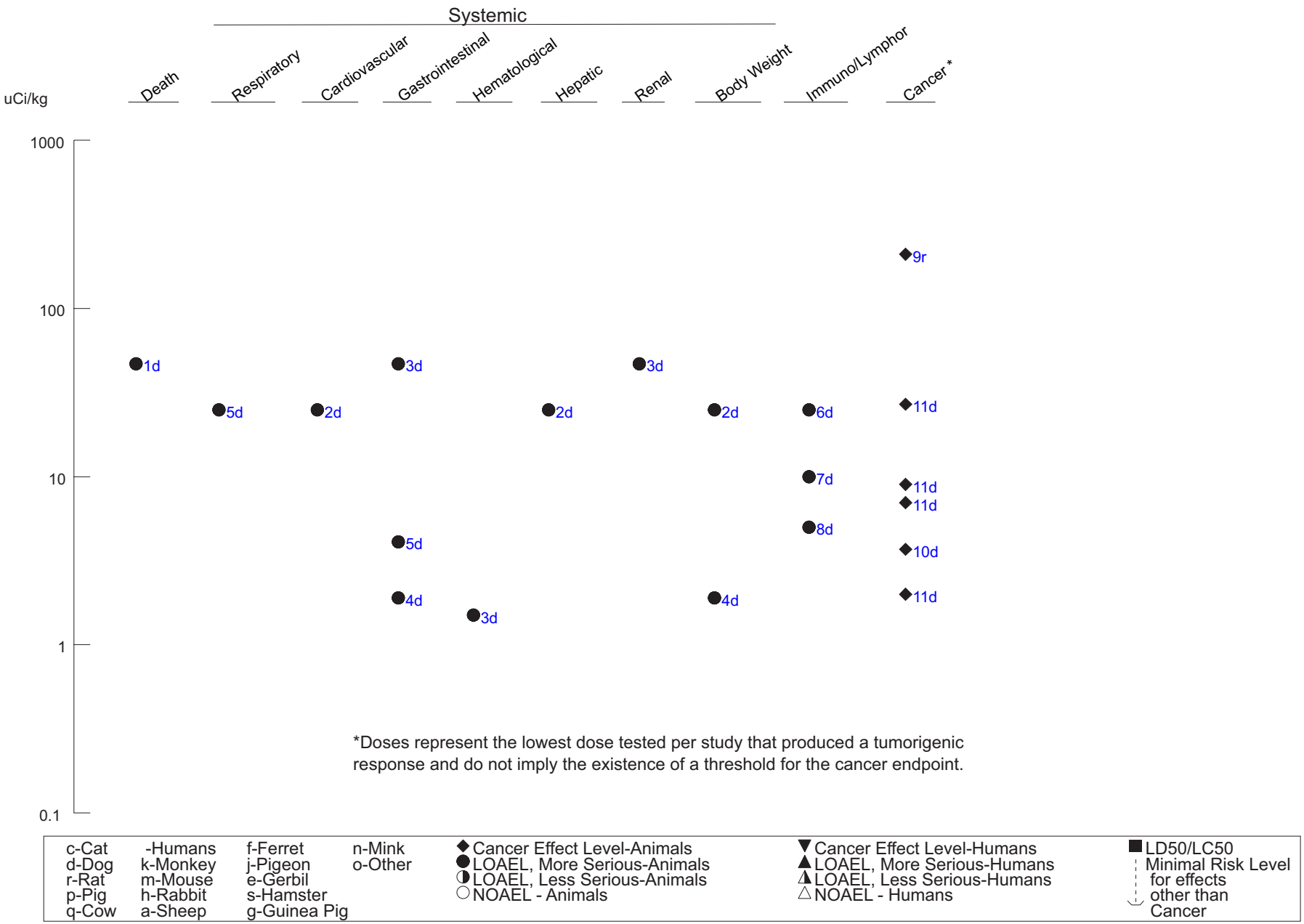
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (µCi/kg)	LOAEL			Reference Chemical Form
					Less Serious (µCi/kg)		Serious (µCi/kg)	
	Cancer							
9	Rat (Holtzman)	once					210 (CEL: osteosarcoma)	Lovelace Foundation 1967 Strontium-90/yttrium-90
10	Dog (Beagle)	once					3.7 [ILB] (CEL: hemangiosarcoma of lung, heart)	Benjamin et al. 1975 Sr-90 (fused-clay particles)
11	Dog (Beagle)	2-22 min once					7 [LTRB] (CEL: osteosarcoma) 9 [LTRB] (CEL: leukemia) 27 [LTRB] (one premature death after 585 days from leukemia) 2 [LTRB] (CEL: nasal carcinoma)	Gillett et al. 1987b Strontium-90 (chloride)

[a] The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; decr = decreased; Gastro = gastrointestinal; (GW) = gavage in water; Hemato = hematological; hr = hour(s); [ILB] = initial lung burden; incr = increased; LOAEL = lowest-observed-adverse-effect level; [LTRB] = long-term retained burden; min = minute(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 3-2 Levels of Significant Exposure to Strontium - Radiation Toxicity - Inhalation

Acute (≤14 days)



Respiratory effects were more pronounced in beagle dogs that were exposed to ^{90}Sr fused-clay particles by inhalation (Benjamin et al. 1976c; Snipes et al. 1979). The primary cause of early death among dogs exposed to initial lung burdens ≥25 μCi ^{90}Sr/kg (925 kBq/kg) was radiation pneumonitis and/or pulmonary fibrosis (Snipes et al. 1979). No such effects were reported in control dogs exposed to nonradioactive aluminosilicate-fused clay particles (Snipes et al. 1979). Clinical signs included an increased respiratory rate, dyspnea, cyanosis, and dry and moist rales (Benjamin et al. 1976c). Radiographically, the dogs showed increased focal or diffuse lung-field densities. The pneumonitis was characterized by acute and chronic inflammation with increased numbers of alveolar macrophages, hypertrophy and hyperplasia of alveolar lining cells, degeneration of the bronchiolar epithelium and alveolar ducts, focal emphysema, and edema. The fibrosis involved the alveolar septa, pleura, and perivascular regions, with substantial scarring. Vascular damage in the lungs was characterized by congestion, hemorrhage (possibly related to thrombocytopenia), fibrin exudation, and occasional vessels with fibrinoid necrosis or intimal proliferation.

Cardiovascular Effects. Acute inhalation of radiostrontium was reported to lead to adverse cardiovascular effects in dogs. Among beagles that died within 5–15 months following inhalation exposure to ^{90}Sr fused-clay particles, most exhibited myocardial necrosis or degeneration, and fibrosis, primarily of the right atrium (Hobbs et al. 1972); these animals had initial lung burdens between 33 and 100 μCi/kg (1.2–3.7 MBq/kg) and cumulative beta radiation doses to the lung of 34,000 to 82,000 rad (340–820 Gy). In a later report of the same study, acute and chronic vascular lesions, characterized as inflammatory or degenerative, affected the elastic and muscular pulmonary arteries in dogs with initial lung burdens between 16 and 94 μCi/kg (0.6–3.5 MBq/kg) and doses to the lung between 40,000 and 96,000 rad (400–960 Gy) at the time of death (Snipes et al. 1977). Vascular damage in the lungs was characterized by congestion, hemorrhage, fibrin exudation, and occasional vessels with fibrinoid necrosis or intimal proliferation (Benjamin et al. 1976c). These effects were attributed to the direct effect of beta radiation (from radiostrontium particles embedded in the lung) on adjacent tissue. In addition, presumably as a consequence of radiation damage to the pulmonary vasculature, the right ventricle became dilated and hypertrophic with congestive heart failure. Hemangiosarcomas resulting from radiostrontium exposure in this study are discussed in Section 3.3.1.7 Cancer.

Gastrointestinal Effects. Gastrointestinal effects were observed in beagle dogs receiving single high doses (long-term retained body burdens between 47 and 83 μCi/kg; 1.74 and 3.07 MBq/kg) of soluble aerosols containing $^{90}SrCl_2$ (Gillett et al. 1987a). Anorexia and, 2 days before death, bloody diarrhea, developed in six dogs that died between 18 and 32 days after the extreme radiation dose rate

induced acute radiation syndrome (Gillett et al. 1987a). It is likely that severe thrombopenia, one of the features of radiation-induced bone marrow hypoplasia, contributed to hemorrhage in the gastrointestinal tract as elsewhere in the body. In addition, some effects could have been due to inhaled $^{90}SrCl_2$ droplets being transported from the mucoid, ciliated nasopharyngeal and tracheobronchial epithelia to the pharynx and then swallowed. The gastrointestinal epithelium then would have been exposed directly to beta emissions from radiostrontium for a day or two. Another report of the same study described three exposed dogs that died at age >11 years with a malabsorption syndrome (Muggenburg et al. 1977). All of the dogs exhibited chronic diarrhea with anorexia, and at necropsy, contained chronic degenerative and inflammatory lesions of the small intestines. Their long-term retained burdens were 1.9–9.6 μCi/kg (70.3–355.2 kBq/kg) and the absorbed doses to the skeleton were calculated to be 530–5,600 rad (5.3–56 Gy). Although the authors could not firmly establish whether the syndrome was a consequence of exposure or of age, the cumulative radiation dose to the digestive tract was likely to have been very low and this argues against ^{90}Sr as the cause.

One beagle dog that was exposed to ^{90}Sr fused-clay particles and had an initial lung burden of 4.1 μCi/kg (151.7 kBq/kg) and a cumulative radiation dose to the lung of 20,000 rad (200 Gy) died 9 years after exposure with anorexia and an ulcerative lesion to the pharynx (Snipes et al. 1979). Whether the pharyngeal lesion was related to exposure is uncertain, since the report was preliminary and no other response to radiation had been observed in this animal.

Hematological Effects. Profound hematological effects were observed in beagle dogs that were exposed once by inhalation either to soluble aerosols containing $^{90}SrCl_2$, or to ^{90}Sr fused to aluminosilicate particles that produced extremely large radiation dose rates and doses in the affected tissues sufficient to induce acute radiation syndrome.

Significant dose-related pancytopenia developed in dogs that were exposed to $^{90}SrCl_2$ aerosols and had long-term retained burdens >10 μCi (370 kBq) ^{90}Sr/kg (Gillett et al. 1987a). Profound decreases in platelet numbers were evident by 7 days and were maximal by 28 days. Drastic thrombocytopenia (platelets reduced >90%) probably contributed to widespread hemorrhaging and premature death in dogs with long-term retained burdens ≥47 μCi/kg (≥1.7 MBq/kg). Significant immediate reductions in platelet counts (>60%) occurred in surviving dogs with long-term retained burdens of ≥1.5 μCi/kg (≥0.56 MBq/kg). However, even dogs with the lowest long-term retained burdens (1–10 μCi/kg; 0.04–0.36 MBq/kg), which otherwise showed little immediate effect, exhibited long-term (>3 years) depression in platelet counts compared to controls. The pattern of neutropenia followed a similar exposure-response,

and profound neutropenia was the most accurate predictor of death. In surviving dogs that were immediately affected by exposure, neutrophil counts recovered, but in these dogs, as well as those immediately unaffected, significant long-term (>3 years) suppression was observed compared to controls. Similarly, lymphocyte counts were drastically reduced (by 75%) in dogs dying within weeks of exposure with long-term retained burdens ≥47 μCi/kg (≥1.7 MBq/kg). Surviving dogs with long-term retained burdens >10 μCi (370 kBq) ^{90}Sr/kg exhibited a long-term (>3 years) suppression of lymphocyte counts (>30%). Dogs with long-term retained burdens between 6 and 10 μCi/kg (0.26–0.36 MBq/kg) exhibited normal lymphocyte counts that were normal over 1,400 days except for periods of significant depression at 60–120 and 900–1,000 days. Dogs with long-term retained burdens between 1 and 3 μCi/kg (0.04–0.12 MBq/kg) had lymphocyte counts that were not significantly different from controls. Reduced erythrocyte mass, as exemplified by decreases in hematocrit, red blood cell counts, and hemoglobin levels, occurred between 2 and 3 weeks after exposure (slightly later than the depression in platelet and white cell counts). In the most severely affected dogs, red blood cell counts fell to 70–80% of pre-exposure values, with maximal depression at 32 days. Prolonged depression of erythrocyte counts was observed in surviving dogs with long-term retained burdens ≥27 μCi/kg (≥1 MBq/kg).

Significant suppression of peripheral lymphocyte counts was observed in beagle dogs that were exposed by inhalation to ^{90}Sr fused-clay particles (Jones et al. 1976). Lymphocytes declined gradually over time in all exposed groups (initial lung burdens ≥5 μCi/kg; ≥185 kBq/kg), and remained more than 50% lower than controls after 2 years.

Hepatic Effects. No studies were located that described hepatic effects in humans following inhalation exposure to radioactive strontium. All beagle dogs that died from radiation pneumonitis following a single inhalation exposure to high concentrations of ^{90}Sr fused-clay particles (25 μCi ^{90}Sr/kg of body weight; 925 kBq/kg) exhibited chronic passive congestion of the liver, and one had mild centrilobular fibrosis (Benjamin et al. 1976c).

Renal Effects. No studies were located that described renal effects in humans following inhalation exposure to radioactive strontium isotopes. Some beagle dogs in the terminal stages of acute radiation syndrome following inhalation exposure to aerosols of $^{90}SrCl_2$ (long-term retained burden 47–83 μCi ^{90}Sr/kg; 1.74–3.07 MBq/kg) had low urine output and elevated blood urea nitrogen (Gillett et al. 1987a).

Body Weight Effects No studies were located that described body weight effects in humans following inhalation of radiostrontium. Anorexia and reduced body weight were observed among beagle dogs with long-term retained burdens between 45 and 119 μCi/kg (1.7–4.4 MBq/kg) following inhalation of $^{90}SrCl_2$ aerosols (Gillett et al. 1987a; Muggenburg et al. 1977) or initial lung burdens between 25 and 32 μCi/kg (0.93–1.2 MBq/kg) following inhalation of ^{90}Sr fused-clay particles (Benjamin et al. 1976c).

3.3.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following inhalation exposure to radioactive strontium isotopes. However, profound effects on the immune system were a consequence of acute inhalation exposure to radiostrontium in dog studies. Effects in dogs exposed to soluble aerosols of $^{90}SrCl_2$ were sequelae of general irradiation of the bone marrow from ^{90}Sr incorporated into bone. Significant dose-related lymphopenia was observed in young adult beagle dogs (12–14 months old) after a single inhalation exposure to $^{90}SrCl_2$ at long-term retained burdens >10 μCi ^{90}Sr/kg (370 kBq/kg; Gillett et al. 1987a). Furthermore, there was some evidence of immunosuppression in dogs with average initial body burdens of 35 μCi ^{90}Sr/kg (1.3 MBq/kg) (Fission Product Inhalation Project 1967a); titers for infectious canine hepatitis and leptospira vaccines were depressed more than 30% following exposure to $^{90}SrCl_2$ aerosols. Effects in dogs exposed to relatively insoluble ^{90}Sr fused-clay particles were primarily a consequence of irradiation of the blood as it circulated through the lungs, although some damage to thoracic lymph nodes was observed. Among beagle dogs (17–20 months old) exposed by nose-only inhalation to ^{90}Sr fused clay particles (initial lung burdens 25–32 μCi ^{90}Sr/kg; 0.925–1.18 MBq/kg), the numbers of peripheral lymphocytes were depressed by more than 50% during the 12th through 28th weeks after exposure, although recovery was observed by week 44 (Benjamin et al. 1976c). The cumulative radiation dose to the lungs ranged from 35,000 to 43,000 rad (350–430 Gy). During the period of lymphocyte suppression, the immune response to phytohemagglutinin antigen tested *in vitro* was depressed 10-fold in the dog that had the highest initial lung burden (32 μCi/kg; 1.18 MBq/kg) and was the first to die. In this animal, the tracheobronchial and sternal lymph nodes, which received a significant radiation dose from ^{90}Sr, were depleted of lymphocytes, although peripheral nodes, which received much lower doses, were nearly normal. In the main study that employed 1-year-old beagles, the highest initial lung burdens of ^{90}Sr fused-clay particles resulted in severe atrophy and fibrosis of the tracheobronchial lymph nodes (Snipes et al. 1977). In other dogs, which had initial lung burdens averaging between 5 and 19 μCi/kg (185 and 703 kBq/kg), fluctuations in the peripheral lymphocyte numbers were observed, but the values remained depressed by 40% for 2 years following inhalation exposure (Jones et al. 1976).

Cumulative doses in these dogs ranged from 1,055 to 4,005 rad (10.5–40 Gy). None of the dog studies reported whether there was a NOAEL identified for immunological effects. Significant chronic suppression of the immune system is considered a serious effect because of the impaired resistance to infectious disease.

3.3.1.4 Neurological Effects

No studies were located that described neurological effects in humans following inhalation exposure to radioactive strontium. A beagle dog that was exposed to the highest concentration of $^{90}SrCl_2$ aerosol (long-term retained burden of 119 μCi/kg or 4.4 MBq/kg) succumbed with epileptic seizures, but the authors deemed these to be unrelated to exposure (Gillett et al. 1987b). Serious neurological effects (convulsions, paralysis) were observed in several dogs that were in the terminal stages of cancer following inhalation of ^{90}Sr fused clay particles (Snipes et al. 1977, 1978). No other studies addressed neurological effects in animals following inhalation exposure to radioactive strontium isotopes.

The highest NOAEL values and all reliable LOAEL values in each species and duration category for neurological effects from exposure to radioactive strontium by the inhalation route are presented in Table 3-2 and plotted in Figure 3-2.

No studies were located regarding the following effects in humans or animals following inhalation exposure to radioactive strontium:

3.3.1.5 Reproductive Effects

3.3.1.6 Developmental Effects

3.3.1.7 Cancer

No studies were located regarding cancer in humans following inhalation exposure to radioactive strontium isotopes, but several studies reported carcinogenetic effects in animals. The types of cancers produced varied with the form of strontium administered. In studies using soluble forms of radioactive strontium, (e.g., $^{90}SrCl_2$), bone-associated cancers were the predominant types, because absorbed strontium primarily incorporates into bone. Studies using relatively insoluble ^{90}Sr fused-clay particles

reported lung-related cancers as the major initial types, since the particles were initially embedded in the lungs. As particles slowly dissolved (releasing ^{90}Sr) or were cleared from the lungs, tumors were induced in other tissues.

In two different experiments described in a report by the Lovelace Foundation (now known as the Lovelace Respiratory Research Institute), young male and female Holtzman rats were exposed once to an aerosol of ^{90}Sr in cesium chloride by whole body inhalation for initial body burdens ranging from 170 to 1,660 μCi ^{90}Sr/kg (6.3–61.4 MBq/kg) of body weight (Fission Product Inhalation Project 1967b). The average skeletal radiation doses over their remaining lifespans averaged from 12,600 to 25,900 rad (126–259 Gy). In the two experiments, 77 or 47% of the rats that died or were euthanized in a moribund state were found to have bone tumors (osteosarcomas). Among rats dying with tumors, the average skeletal dose rate was 81 rad/day, compared to 62 rad/day for rats without tumors (0.81 vs 0.62 Gy/day).

Primary bone cancer was the most frequent cause of death in beagle dogs (30/66) given a single inhalation exposure to $^{90}SrCl_2$ aerosol and then observed for their lifespans (Benjamin et al. 1974a, 1976a, 1979; Gillett et al. 1987b; McClellan et al. 1973; Muggenburg et al. 1977, 1978, 1979). The cumulative absorbed doses of beta radiation to bone ranged from 12 to 1,200 rad (0.012–12 Gy) at 30 days and from 200 to 170,000 rad (2–1,700 Gy) at 1,000 days after exposure. In dogs with bone-related tumors, the long-term retained burdens ranged from 2 to 119 μCi ^{90}Sr/kg (0.081–4.4 MBq/kg) of body weight. Bone-tumor-related deaths occurred 759–3,472 days after exposure (median survival time of 1,702 days, compared to 4,500 days for controls). Twenty-seven tumors were classified as different subtypes of osteosarcoma, 14 as hemangiosarcomas, 3 as fibrosarcomas, and 1 as a myxosarcoma. 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 (Benjamin et al. 1979). In addition, two dogs died from myelomonocytic leukemia resulting from irradiation of bone marrow. Metastasis occurred from 21 tumors, in particular the hemangiosarcomas, with the lungs being the most frequent site of metastasis (76%).

Among 127 beagle dogs exposed by inhalation to ^{90}Sr fused-clay particles, deaths from primary pulmonary tumors were common: 19 dogs with hemangiosarcomas (one each also with bronchioalveolar carcinoma, nasal squamous cell carcinoma, or pulmonary epidermoid carcinoma), and one with pulmonary squamous cell carcinoma (Snipes et al. 1979). All 34 dogs exposed to ^{90}Sr fused clay particles with cumulative exposures of >29,000 rad (290 Gy) developed pulmonary hemangiosarcoma. The heart wall was the other primary location of hemangiosarcoma (11 dogs), the others being the mediastinum,

spleen, rib, lung-associated lymph nodes, and liver (Snipes et al. 1979). Hemangiosarcomas were metastatic in all but one affected dog. Among dogs dying prematurely from neoplasms of the lung, the initial lung burdens were 3.7–94 μCi/kg (0.14–3.5 MBq/kg) and the estimated cumulative doses to the lungs ranged from 43,000 to 67,000 rad (430–670 Gy) (Benjamin et al. 1975). Considering all dogs with tumors, pulmonary carcinomas or sarcomas occurred in 3/12 dogs that received cumulative radiation doses of 17,000–25,000 rad (170–250 Gy), but no pulmonary tumors were reported for three dogs with cumulative exposure levels of 11,000–15,000 rad (110–150 Gy; Hahn et al. 1983a).

The highest NOAEL values and all reliable LOAEL values in each species and duration category for cancer effects from exposure to radioactive strontium by the inhalation route are presented in Table 3-2 and plotted in Figure 3-2.

3.3.2 Oral Exposure

Upon ingestion, radioactive strontium isotopes become incorporated into bone, and irradiate the surrounding hard and soft tissues, resulting in hypoplasia of the bone marrow or various forms of cancer (osteosarcoma, leukemia). Adverse effects are associated with higher skeletal burdens of radioactive strontium. Younger organisms are more vulnerable to adverse effects of both stable and radioactive strontium. Maternal oral exposure to sufficient radioactive strontium can adversely affect the fetus.

The database for oral exposures to radioactive strontium is substantial. Human health effect data are derived primarily from long-term and ongoing studies of a population that was exposed to contaminated drinking water and food following the release of large quantities of radioactive materials into the Techa River from a Soviet nuclear weapons facility between 1949 and 1956. This population received a mixed exposure to external gamma radiation and to internal radiation from ^{89}Sr, ^{90}Sr, and ^{137}Cs (Akleyev et al. 1995; Kossenko et al. 2000). Animal data include several large, long-term studies in dogs, miniature pigs, and rodents. In addition to the papers cited below, interim reports and analyses for the beagle lifetime study (Laboratory for Energy-Related Health Research at the University of California at Davis) were published by Nilsson and Book (1987), Nilsson et al. (1985), Pool et al. (1972, 1973b), and Raabe et al. (1981a, 1981b, 1983, 1994).

3.3.2.1 Death

In the Techa River population that was exposed to radiostrontium and radiocesium in drinking water and food between 1949 and 1956, an increase in the number of deaths from leukemia and solid cancers was reported (Kossenko 1996). In the exposed group, the standardized mortality rate was 140 (95% CI: 131–150) per 100,000 compared to 105 (95% CI: 101–109) per 100,000 in the control group during the followup period (1950–1982). Absorbed doses to the red bone marrow in the study group were between 17.6 and 164 rad (0.176 and 1.64 Gy). No increase in cancer mortality was observed among offspring of exposed individuals. These data are omitted from Table 3-3 because the exposures were to multiple sources of radiation.

Oral exposure to radioactive strontium caused dose-related increases in mortality in animal studies. In general, younger animals were more sensitive to the effects of radiation than older animals. There was an increase in deaths in a small number (6 out of 7) of Rhesus monkeys given 100 μCi of ^{90}Sr per day (3.7 MBq/day) by gavage for 5 or 10 days (Casarett et al. 1962). One monkey given 11 μCi/kg/day (0.42 MBq/kg/day) for 5 days died 4 years after treatment from leukemia with a total skeletal dose of 4,300 rad (43 Gy). One monkey given a dose of 28 μCi/kg/day (1.0 MBq/kg/day) for 10 days died within 4 months of treatment from pancytopenia with an estimated skeletal dose of 4,500 rad (45 Gy). Two others exposed to an average of 18 μCi/kg/day (0.67 MBq/kg/day) for 10 days died from bone associated cancers within 36 months of treatment, and with estimated skeletal doses of 4,700–9,500 rad (47–95 Gy). Because of the small sample size and the fact that the animals were of different ages, this study serves as an indicator, but not as proof of dose-response effects of ingested radiostrontium.

In experiments in which weanling (30 days old) and adult Long-Evans rats were given ^{90}Sr in drinking water for 10 days, survival at 5 months was reduced by 80% in the weanlings consuming at least 297–386 μCi ^{90}Sr/kg/day (11 MBq/kg/day; total 464 μCi or 17 MBq), but was unaffected in adults consuming 64–194 μCi ^{90}Sr/kg/day (7.2 MBq/kg/day; total 650 μCi or 24.1 MBq; Casarett et al. 1962). The reduced survival of the weanlings was consistent with their higher skeletal burden at 5 months: >20 times higher than in the adults. In another acute study, six young female dairy cattle (three sets of twins from three different strains, ages 398 and 479 days and weighing 145–349 kg at the start of treatment) were given 44 μCi ^{90}Sr/kg/day (1.63 MBq/kg/day) 'orally' for 5 days (Cragle et al. 1969). The four youngest (398 days) and lightest heifers (145–212 kg), which were administered a total of 32–46 mCi (1.18–1.70 GBq), died of radiation sickness between 93 and 132 days after treatment was started, whereas the older and heavier animals (342–349 kg), which had received a total of 75–77 mCi of ^{90}Sr (2.78–

2.85 GBq), were still alive 3 years after treatment. In addition to age-related differences, strain differences may have contributed to the results; the older cows were Holsteins, which have more massive skeletons than the Brown Swiss and Jersey strains. The authors suggested that the larger animals survived because of the wider diameter of the marrow cavity, which possibly shielded the central marrow from beta radiation released from ^{90}Sr (and its ^{90}Y decay product) deposited at the periphery of the bone shaft.

In an intermediate-duration experiment, young (87-day-old) Long-Evans rats were treated with up to 104 μCi of ^{90}Sr per kg of body weight per day (3.8 MBq/kg/day) for 30 days over a period of 37 days (Casarett et al. 1962; Hopkins et al. 1966); the total amount administered was 790 μCi (29.2 MBq). In these rats, the estimated skeletal activity of ^{90}Sr at 5 months was 11 μCi (407 kBq) and survival was reduced by about 36%. In the young rats treated for 30 days, skeletal activity was higher and survival was reduced accordingly compared to the adult rats treated for 10 days (see previous paragraph), but the differences were out of proportion to the total amounts of ^{90}Sr administered to the two sets of rats. The total amount given to adults was 18% less than to the juveniles, but the skeletal doses in the adults were 82% less, suggesting age-related differences in incorporation.

In a lifetime study, adult CF-1 mice that were exposed to ^{90}Sr beginning at ages 110–250 days were less vulnerable to continuous exposure than mice that had been exposed since conception (Finkel et al. 1960). The adult lifespan was shortened by 17% in mice given 31 μCi ^{90}Sr/kg/day (1.15 MBq/kg/day), but was unaffected by administration of up to 16 μCi ^{90}Sr/kg/day (592 kBq/kg/day). In mice exposed from conception, the lifetime was shortened by 40% when given 36 μCi ^{90}Sr/kg/day (1.33 MBq/kg/day), and by 26% when given between 4 and 19 μCi ^{90}Sr/kg/day (148 and 703 kBq/kg/day), but was unaffected by 0.05–0.4 μCi ^{90}Sr/kg/day (1.85–14.8 kBq/kg/day). In albino rats that were fed 0.5 or 2 μCi ^{90}Sr/kg/day (18.5 or 74 kBq/kg/day) for their postweaning lifetime, the lifespan was shortened, by about 18 or 30%, respectively, compared to controls (Zapol'skaya et al. 1974). The authors calculated that the lifespan was shortened by 0.09 day per rad. A plot of mortality against absorbed dose showed maximum mortality (40%) against a skeletal absorbed dose of 4,000 rad (40 Gy). In a study in which eight weanling Dutch rabbits were fed approximately 6 μCi/kg/day (218 kBq/kg/day) in pellets once a day for 31–280 days, some died within a few weeks with bone marrow that was slightly hypoplastic (Downie et al. 1959). The bone marrow was entirely atrophic in rabbits dying several months later with osteogenic sarcoma.

Two related long-term oral exposure studies demonstrated dose-related effects of $^{90}SrCl_2$ on survival in beagle dogs. In the main study, groups of pregnant beagles were fed 0.002–3.6 μCi ^{90}Sr/kg/day (0.074–

133.2 kBq/kg/day) from gestational day 21 through lactation to postnatal day 44, and the pups were fed the same doses from weaning at day 42 through day 540 (Raabe et al. 1983; White et al. 1993). Survival of the pups was reduced by 18, 64, and 85% at the three highest levels (0.4, 1.2, and 3.6 μCi/kg/day or 14.8, 44.4, and 133.2 kBq/kg/day, respectively). Survival was not significantly different from the controls for exposures of 0.002–0.13 μCi/kg/day (0.074–4.8 kBq/kg/day). Mean absorbed skeletal absorbed doses at or below 2,250 rad (22.5 Gy) had no effect on mortality, whereas increased mortality was observed at or above 5,040 rad (50.4 Gy). The secondary study had a similar protocol, except that the dogs were given doses of 0.13–1.2 μCi/day (4.81–44.4 kBq/day) from gestational day 21 throughout their entire lifetime (Book et al. 1982). The mean lifetime absorbed skeletal doses were 2,840–11,190 rad (28.4–111.9 Gy). The median lifespans were reduced by 11–65%, which was similar to the results of the main study. This implies that irradiation after day 540 did not significantly change the survival rate and that survival was shortened because of exposure at a young age. The two main radiation-related causes of death in these studies were myeloproliferative syndrome and skeletal sarcomas (see Section 3.3.2.7 Cancer).

In a multigenerational study of female Pitman-Moore miniature swine, there were dose-related effects on mortality following chronic ingestion of ^{90}Sr in the form of strontium chloride (Clarke et al. 1970; McClellan et al. 1963; Ragan et al. 1973). Sows ingesting 3,100 μCi ^{90}Sr/day (114.7 MBq/day) from age 9 months did not survive their first pregnancy, succumbing from the destruction of hemopoietic tissue in the bone marrow. The sows developed anemia, leukopenia, thrombocytopenia, and terminal hemorrhagic syndrome (Clarke et al. 1972). Exposure to 25, 125, or 625 μCi ^{90}Sr/day (0.925, 4.625, or 23.13 MBq/day) significantly increased mortality after 11, 5, and 1 year(s), respectively, whereas exposure to 1 or 5 μCi ^{90}Sr/day (37 or 185 kBq/day) had no effect on survival. Effects on the F1 females exposed from the time of conception were more severe, even though, after weaning, their administered dose level was only a fraction of the maternal level until the age of 6 months. None of the F1 females exposed to 625 μCi ^{90}Sr/day (23.13 MBq/day) survived to the age of 9 months, whereas that dose was not immediately fatal to the parental generation of sows. Furthermore, the F1 females receiving 25 μCi ^{90}Sr/day (925 kBq/day) showed a significant increase in cumulative mortality after 7 years, rather than 11. However, the 1 and 5 μCi ^{90}Sr/day levels (37 and 185 kBq/day), as in the parental generation, had no effect on survival. In this study, the average attained body burden was 10, 50, 250, 1,250, and 4,700 μCi (0.37, 1.85, 9.25, 46.25, and 173.9 MBq) for the 1, 5, 25, 125, and 625 μCi ^{90}Sr/day (0.037, 0.185, 0.925, 4.625, and 23.13 MBq/day) levels, respectively.

All reliable LOAEL values for death from oral exposure to radioactive strontium in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.3.2.2 Systemic Effects

No studies were located regarding endocrine, dermal, or metabolic effects in humans or animals after oral exposure to radioactive strontium. The highest reliable NOAEL and all LOAEL values for the systemic effects from oral exposure to radioactive strontium are shown in Table 3-3 and plotted in Figure 3-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to radioactive strontium isotopes. No studies were located regarding respiratory effects in animals following acute- or intermediate-duration exposure to radioactive strontium. In a chronic-duration beagle study, animals exposed to 0.4 or 1.2 µCi/kg/day (14.8 or 44.4 kBq/kg/day) of ^{90}Sr *in utero* from gestational day 21, throughout lactation, and from weaning on day 42 to day 540 exhibited only secondary respiratory effects (Dungworth et al. 1969); lungs showed varying degrees of myeloid infiltration (see Section 3.3.2.7 Cancer). Since this effect is not the direct result of the action of radiostrontium on lung tissue, but rather a secondary effect of myeloid proliferation induced by irradiation of bone marrow, it is not categorized under Systemic: Respiratory Effects in Table 3-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to radioactive strontium isotopes. No studies were located regarding cardiovascular effects in animals after acute- or intermediate-duration oral exposure to radioactive strontium isotopes. Petechiae, ecchymoses, and gastrointestinal bleeding were found postmortem in some beagles in a chronic-duration study, in which animals were exposed to 0.002–1.2 µCi ^{90}Sr/kg/day (0.074–44.4 kBq/kg/day) *in utero* from gestational day 21, throughout lactation, and from weaning on day 42 to day 540 (Dungworth et al. 1969). These findings, observed in high dose animals (0.4 and 1.2 µCi/kg/day; 14.8 and 44.4 kBq/kg/day), indicated the presence of a hemorrhagic disorder related to thrombocytopenia (see Hematological Effects below).

The highest reliable NOAEL and all LOAEL values for cardiovascular effects from oral exposure to radioactive strontium in each species and duration category are shown in Table 3-3 and plotted in Figure 3-3.

Table 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (uCi/kg/day)	LOAEL Less Serious (uCi/kg/day)	LOAEL Serious (uCi/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Monkey (Rhesus)	5-10 d (GW)				28 M (1/1 dead within 4 months from pancytopenia; est skeletal dose at death =4,500 rad)	Casarett et al. 1962 Strontium-90
2	Rat (Long- Evans)	10 d ad lib (W)				297 M (lifespan decr 80%)	Casarett et al. 1962 Strontium-90
3	Cow	5 d 1 x/d				44 F (4/6 died within 5 months)	Cragle et al. 1969 Strontium-90
	Systemic						
4	Rat (Long- Evans)	10 d ad lib (W)	Hemato			297 M (hypoplasia of bone marrow)	Casarett et al. 1962 Strontium-90
			Musc/skel			297 M (failure of osteogenesis)	
5	Rat (Long- Evans)	10 d ad lib (W)	Hemato		64 M (slight hypoplasia of bone marrow)		Casarett et al. 1962 Strontium-90
6	Cow	5 d 1 x/d	Gastro			44 F (intestinal hemorrhage)	Cragle et al. 1969 Strontium-90
			Hemato			44 F (severe leukopenia, thrombocytopenia)	
	Reproductive						
7	Rat	once (G)				0.15 F (20% fetal mortality)	Howard and Clarke 1970 Strontium-90

Table 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (uCi/kg/day)	LOAEL Less Serious (uCi/kg/day)	LOAEL Serious (uCi/kg/day)		Reference Chemical Form
	Cancer							
8	Monkey (Rhesus)	5-10 d 1 x/d (GW)				11	(CEL: leukemia in 1/1)	Casarett et al. 1962 Strontium-90
9	Rat (Long- Evans)	10 d ad lib (W)				300 M	(CEL: osteosarcoma)	Casarett et al. 1962 Strontium-90
10	Rat (Long- Evans)	10 d ad lib (W)				135 M	(CEL: 2 x incr in incidence of malignancies)	Casarett et al. 1962 Strontium-90
	INTERMEDIATE EXPOSURE							
	Death							
11	Rat (Long- Evans)	30 d ad lib (W)				74 M	(35% decr survival)	Casarett et al. 1962 Strontium-90
12	Rabbit (Dutch)	31-280 d 1 x/d (F)				6	(premature death from bone marrow hypoplasia)	Downie et al. 1959 Strontium-90
	Systemic							
13	Rat (Long- Evans)	30 d ad lib (W)	Hemato			74 M	(moderate bone marrow hypoplasia)	Casarett et al. 1962 Strontium-90
			Musc/skel			74 M	(damaged epiphyseal cartilage)	
14	Rabbit (Dutch)	31-280 d 1 x/d (F)	Hemato			6	(bone marrow hypoplasia; anemia, reduced platelets)	Downie et al. 1959 Strontium-90
			Musc/skel			6	(decr osteocytes, decr blood vessels of bone)	

Table 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (uCi/kg/day)	LOAEL Less Serious (uCi/kg/day)	LOAEL Serious (uCi/kg/day)	Reference Chemical Form
	Reproductive						
15	Mouse (CF-1)	600 d ad lib (F)		31 F			Finkel et al. 1960 Strontium-90
	Cancer						
16	Rat (Long- Evans)	30 d ad lib (W)				74 M (CEL: 28% osteosarcoma, 11% skin carcinoma, 6% leukemia compared to none in control group)	Casarett et al. 1962 Strontium-90
17	Rat (Long- Evans)	37 d 1 x 30 d ad lib (W)				74 F (CEL: osteosarcoma)	Hopkins et al. 1966 90Sr
18	Rabbit (Dutch)	31-280 d 1 x/d (F)				6 (CEL: osteosarcoma; multiple myeloma)	Downie et al. 1959 Strontium-90
	CHRONIC EXPOSURE						
	Death						
19	Rat (albino)	372-620 d daily ad lib (F)				0.5 (18% mortality)	Zapol'skaya et al. 1974 Strontium-90
20	Mouse (CF-1)	600 d ad lib (F)				31 F (survival decr 17%)	Finkel et al. 1960 Strontium-90
21	Mouse (CF-1)	GD0-PND 414 ad lib (F)				4 F (survival decr 36%)	Finkel et al. 1960 Strontium-90

Table 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (uCi/kg/day)	LOAEL Less Serious (uCi/kg/day)	LOAEL Serious (uCi/kg/day)	Reference Chemical Form
	Systemic						
22	Rat (albino)	372-620 d daily ad lib (F)	Hemato			0.5 (~21% leukopenia lasting 2 yrs)	Zapol'skaya et al. 1974 Strontium-90
23	Mouse (CF-1)	GD0-PND 414 ad lib (F)	Bd Wt	36 F			Finkel et al. 1960 Strontium-90
24	Dog (Beagle)	GD40-death ad lib (F)	Musc/skel			0.4 M (osteodystrophy)	Book et al. 1982 Strontium-90
25	Dog (Beagle)	GD40-PND540 ad lib (F)	Cardio			0.4 M (petechiae, ecchymoses, gastrointestinal bleeding)	Dungworth et al. 1969 Strontium-90
			Hemato			0.4 M (leukopenia, anemia, thrombocytopenia; poikilocytosis, anisocytosis, hypochromasia of erythrocytes)	
			Hepatic			0.4 M (periacinar lipidosis; terminal necrosis)	
			Bd Wt			0.4 M (progressive weight loss in anemic dogs)	
26	Dog (Beagle)	GD40-PND540 ad lib (F)	Musc/skel			0.4 M (osteolytic lesions, osteoporosis, cortical sclerosis and thickening, mottling)	Momeni et al. 1976 Strontium-90

Table 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (continued)

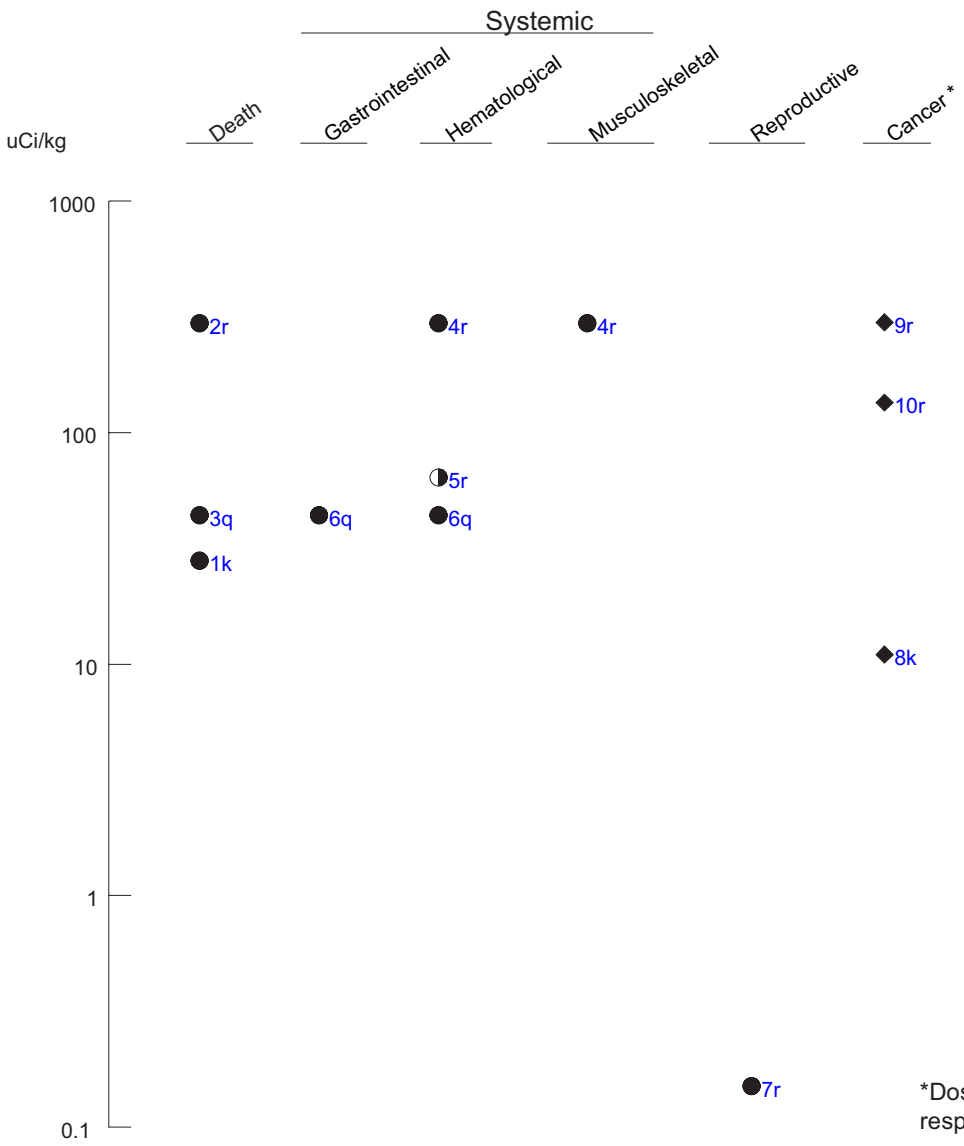
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (uCi/kg/day)	LOAEL Less Serious (uCi/kg/day)	LOAEL Serious (uCi/kg/day)	Reference Chemical Form
	Immuno/ Lymphoret						
27	Dog (Beagle)	GD40-PND540 ad lib (F)				0.4 M (splenic myeloid metaplasia)	Dungworth et al. 1969 Strontium-90
	Developmental						
28	Mouse (CF-1)	600 d ad lib (F)				3 F (decr postnatal survival from cancer)	Finkel et al. 1960 Strontium-90
	Cancer						
29	Rat (albino)	372-620 d daily ad lib (F)				2 (CEL: lymphosarcoma, osteosarcoma)	Zapol'skaya et al. 1974 Strontium-90
30	Mouse (CF-1)	600 d ad lib (F)				0.03 F (CEL: reticular tumors)	Finkel et al. 1960 Strontium-90
31	Mouse (CF-1)	GD0-PND 414 ad lib (F)				36 F (CEL: 4x incr reticulocyte tumors; osteosarcoma)	Finkel et al. 1960 Strontium-90
32	Dog (Beagle)	GD40-death ad lib (F)				0.4 M (premature death from cancer)	Book et al. 1982 Strontium-90
33	Dog (Beagle)	GD40-PND540 ad lib (F)				1.3 M (CEL: osteosarcoma) 0.4 M (incr death from cancer)	White et al. 1993 Strontium-90

[a] The number corresponds to entries in Figure 3-3.

Ad lib - ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; (F) = food; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; (GW) = gavage in water; Hemato = hematological; incr = increased; LOAEL = lowest-observed-adverse-effect level; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PND = post natal day; (W) = water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral

Acute (≤14 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (*Continued*)

Intermediate (15-364 days)

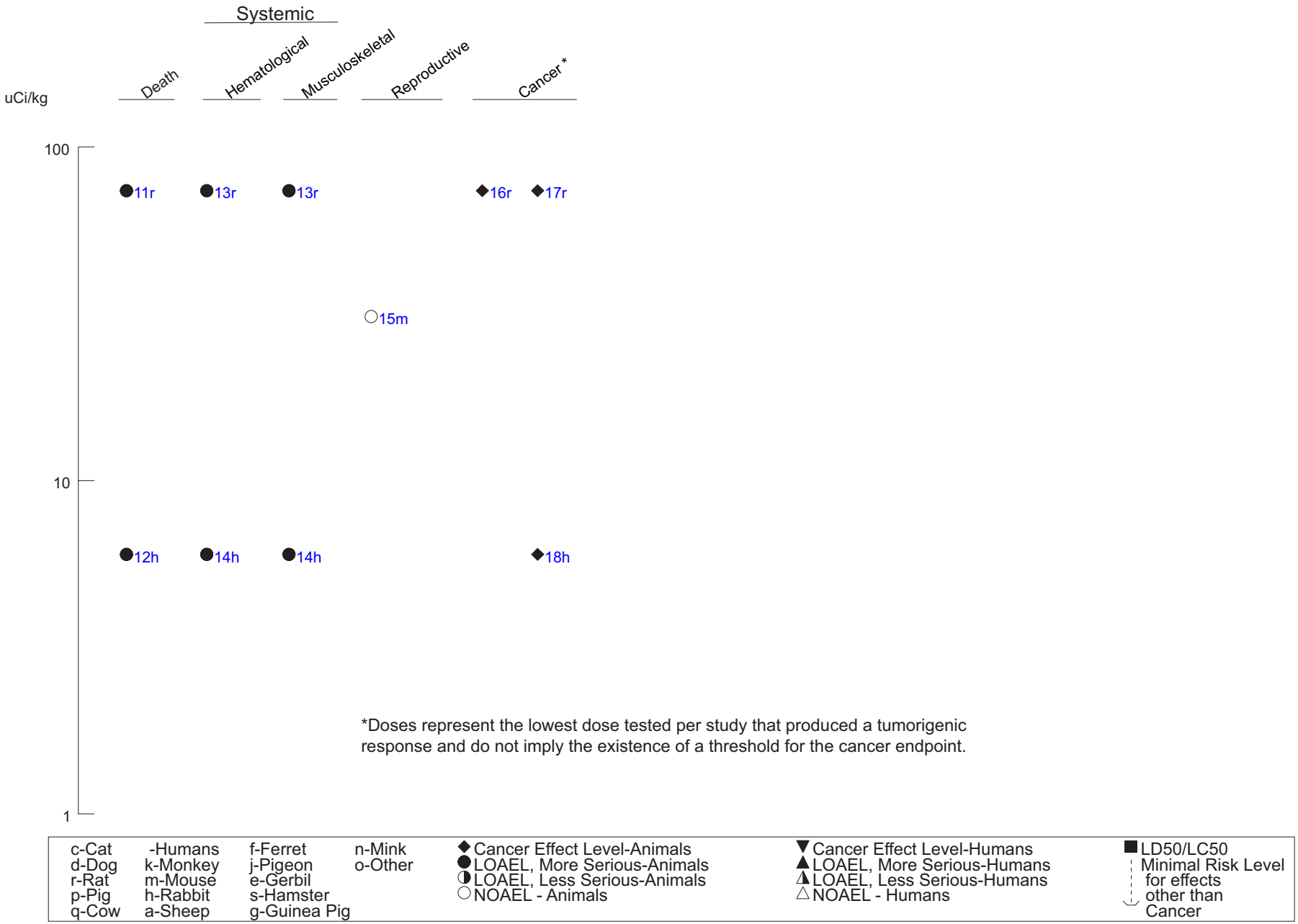
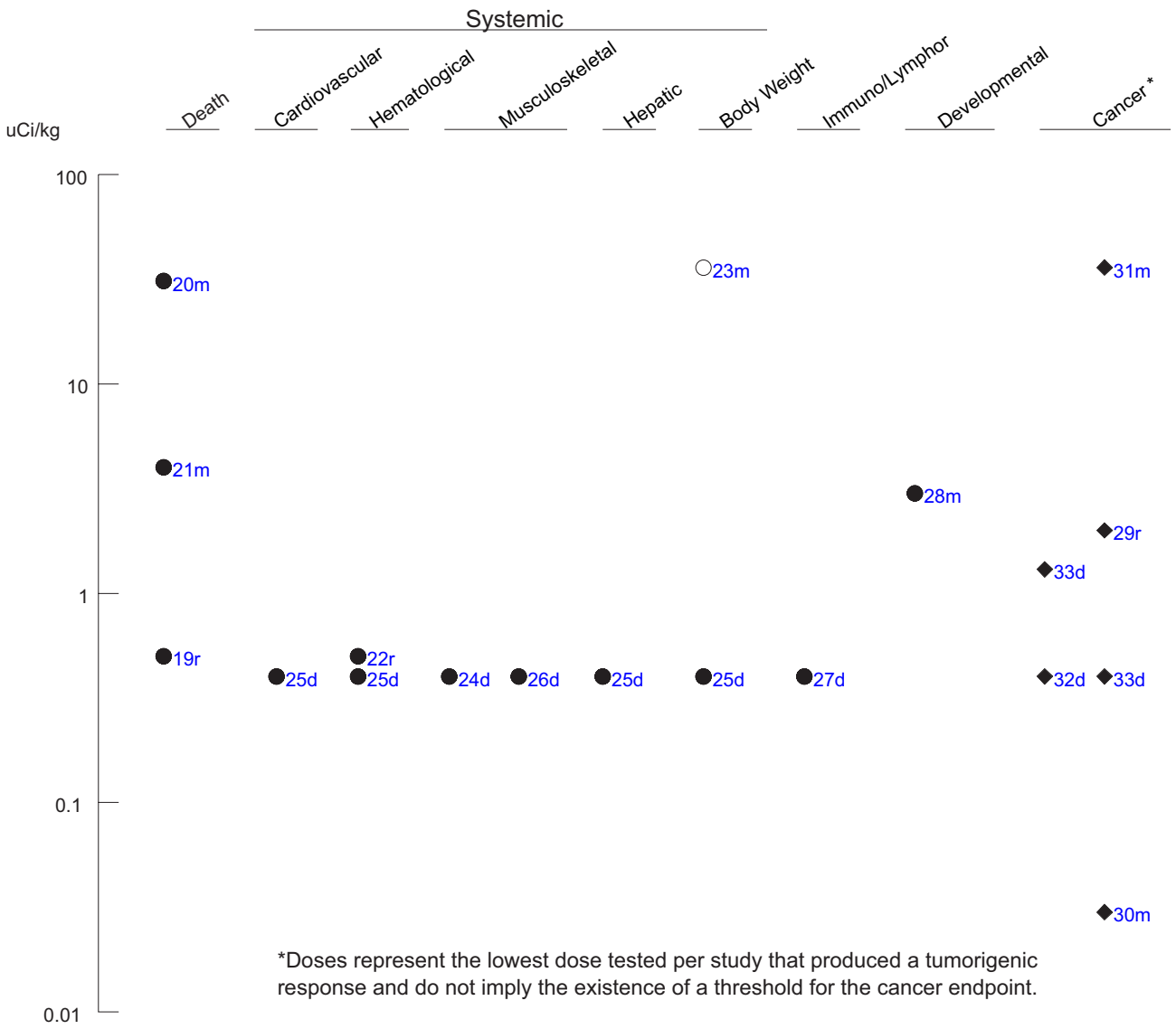


Figure 3-3 Levels of Significant Exposure to Strontium - Radiation Toxicity - Oral (*Continued*)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to radioactive strontium. Intestinal hemorrhage occurred in cows succumbing to radiation sickness 3 months after ingesting 44 μCi ^{90}Sr/kg/day (1.63 MBq/kg/day) for 5 days (Cragle et al. 1969). It is likely that other reports of terminal hemorrhagic effects (see Hematological Effects below) following high doses of radiostrontium encompassed intestinal hemorrhage whether or not it was specifically mentioned.

Hematological Effects. In human and animal studies, adverse hematological affects were associated with beta radiation of bone marrow following incorporation of radiostrontium into bone.

The Techa River population exposed to chronic combined external gamma radiation and internal radiation due to ^{90}Sr and ^{137}Cs exhibited alterations in hematological parameters, including leukopenia, thrombocytopenia, and granulocytopenia (Akleyev et al. 1995). These effects were observed in a portion of the exposed population that received radiation doses to the bone marrow at rates in excess of 30–50 rem (0.3–0.5 Sv) per year. These data are omitted from Table 3-3 because exposures were to multiple sources of radiation.

Among Rhesus monkeys given 1,000 μCi (37 MBq) of ^{90}Sr over 10 days, the one with the highest dose on a kg body weight basis (28 μCi/kg/day; 1.0 MBq/kg/day) died from pancytopenia within 4 months of treatment (Casarett et al. 1962). Among young (30 days old) Long-Evans rats that were given >300 μCi ^{90}Sr/kg/day (11 MBq/kg/day) in drinking water for 10 days (total 460 μCi; 17 MBq), the bone marrow was extremely hypoplastic. Hypoplastic effects were slight among adult males given doses of 64 or 135 μCi/kg/day or adult females given 92 or 194 μCi/kg/day (total 330 or 650 μCi; total 12.2 or 24.1 MBq; Casarett et al. 1962). Skeletal radiation doses were about 15 times higher in the younger rats. In another acute study, six young female dairy cattle (three sets of twins, ages 398 and 479 days and weighing 145–349 kg at the start of treatment) were given 44 μCi ^{90}Sr/kg/day (1.63 MBq/kg/day) for 5 days (Cragle et al. 1969). All six heifers exhibited decreases in leukocyte and platelet counts by the first month. In surviving animals, the counts plateaued at about 60% of the normal value. In four animals, the youngest (398 days old) and lightest (145–212 kg) at the time of dosing, leukocyte and platelet counts dropped severely after 80 days, shortly before the onset of the terminal stages of radiation sickness.

In an intermediate-duration study in young Long-Evans rats, moderate hypoplasia of the bone marrow occurred among males (87 days old) given 74 μCi/kg/day and females given 104 μCi/kg/day (2.7 and

3.8 MBq/kg/day, respectively) of ^{90}Sr in drinking water for 30 days (total 790 μCi; 29.2 MBq) (Casarett et al. 1962). Hypoplasia of the bone marrow leading to anemia and thrombocytopenia developed in Dutch rabbits that were fed approximately 6 μCi ^{90}Sr/kg/day (218 kBq/kg/day) in pellets for 31–280 days (Downie et al. 1959).

Chronic-duration studies in several species reported suppression of hematopoiesis. In albino rats fed ≥0.5 μCi ^{90}Sr/kg/day (18.5 kBq/kg/day) for their post-weaning lifetime, hematopoiesis was significantly depressed (Zapol'skaya et al. 1974). Lymphocytes were the first cells affected, then neutrophils, thrombocytes, and after 1 year, erythrocytes. Morphological abnormalities included binucleation. At 0.5 μCi ^{90}Sr/kg/day (18.5 kBq/kg/day), leukocyte numbers remained 20% depressed by the end of the second year. The authors calculated that the minimal dose to induce leukopenia was 150–200 rad. The reduction in leucocytes plateaued at about 30–35% for absorbed doses between 400 and 2,000 rad. Hematological effects were reported in a chronic-duration beagle study, in which animals were exposed to 0.002–1.2 μCi/kg/day (0.074–44.4 kBq/kg/day) of ^{90}Sr *in utero* from gestational day 21, throughout lactation, and from weaning on day 42 to day 540 (Dungworth et al. 1969). Six years after exposure began, the following effects were observed at doses of 0.44 or 1.2 μCi/kg/day (14.8 or 44.4 kBq/kg/day): abnormal erythrocyte morphology (primarily poikilocytosis, anisocytosis, and hypochromasia, with some instances of macrocytosis), dose-related, radiation-induced leukopenia, an abnormal number of immature granulocytes, one case of unusual giant neutophils, a reduction in the number of platelets, anemia, and splenomegaly. Similarly, female Pitman-Moore miniature swine exposed to 3,100 μCi ^{90}Sr/day (114.7 MBq/day) as strontium chloride died within 3–4 months from destruction of hematopoietic tissue in bone marrow, which resulted in anemia, leukopenia, thrombocytopenia, and terminal hemorrhagic syndrome (Clarke et al. 1972). In addition, two animals in this group developed myeloid metaplasia.

Musculoskeletal Effects. Skeletal effects following oral exposure to radioactive strontium have been reported in humans and animals. Dystrophic lesions of the skeleton, primarily affecting articular and periarticular tissues, were observed in the Techa River populations that were chronically exposed to radiostrontium and other radionuclides in contaminated food and water (Akleyev et al. 1995). The incidence of skeletal lesions was significantly higher for mean radiation doses to the surface of bone in excess of 200 rem (2 Sv).

In an acute uptake, chronic radiation study, male and female 30-day-old Long-Evans rats that were given 300 or 390 μCi ^{90}Sr/kg/day, respectively (11 or 14.4 MBq/kg/day) in drinking water for 5–10 days (total 460 μCi; 17 MBq) exhibited signs of abnormal osteogenesis more than 10 months after administration

(Casarett et al. 1962). As marrow failed to invade into metaphyseal cartilage, the cartilage resumed active proliferation. Resorption failed to occur in metaphyseal cartilage and metaphyseal spongiosa failed to transform to lamellar bone. Often, cartilage and fibrous marrow were incorporated into cortical bone, sometimes causing fracture and deformation.

In an intermediate uptake, chronic radiation study on young (87 days old) Long-Evans rats, ingestion of 74 (males) or 104 (females) μCi ^{90}Sr /kg/day (2.7 or 3.8 MBq/kg/day) in drinking water for 30 days (total 790 μCi; 28.9 MBq) adversely affected the vasculature of the bone, which interfered with the normal transformation of cartilage into bone (Casarett et al. 1962). At the end of the long bones, the cartilage discs were damaged, with detachment of primary spongiosa and failure of resorption. In another intermediate-duration study, numbers of osteocytes (bone cells surrounded by a mineralized matrix and connected by a mesh-work of processes) were reduced in Dutch rabbits that ingested approximately 6 μCi ^{90}Sr/kg/day (218 kBq/kg/day) in pellets for 48 days (Downie et al. 1959).

Bone damage was a notable effect of chronic-duration oral exposure to radioactive strontium in dogs (Momeni et al. 1976). Groups of pregnant beagles were fed 0.002–3.6 μCi ^{90}Sr/kg/day (0.074–133.2 kBq/kg/day) from gestational day 21 through lactation to PND 44, and the pups were fed the same doses from weaning at day 42 through day 540 (Raabe et al. 1983; White et al. 1993). Ten years from the start of the study, dose-related skeletal effects included mild trabecular osteopenia, endosteal and periosteal cortical changes (sclerosis and thickening), and mottling or focal osteolytic lesions (Momeni et al. 1976). These occurred in all the dogs in the 3.6 μCi/kg/day group and also in the 1.2 and 0.4 μCi/kg/day groups (133.2, 44.4, and 14.8 kBq/kg/day, respectively). Radiation-induced osteodystrophy was noted in three out of four beagle dogs that received 1.2 μCi ^{90}Sr/kg/day (44.4 kBq/kg/day) for life beginning at midgestion (Book et al. 1982); the average dose rate (cumulative dose divided by lifespan) for these dogs was 4 rad/day (0.04 Gy/day). Radiation osteonecrosis was said to be a common finding among female Pitman-Moore miniature swine that died with hematopoietic disorders or bone marrow hypoplasia after ingesting $^{90}SrCl_2$ at levels between 1 and 3,100 μCi/day (0.37–114.7 MBq/day) until death (Clarke et al. 1972). The incidence of osteonecrosis at each dose level was not reported. Bone cancers that were reported in these chronic studies are discussed below in Section 3.3.2.7.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to radioactive strontium isotopes. No studies were located regarding hepatic effects in animals after acute- or intermediate-duration oral exposure to radioactive strontium isotopes. In a chronic-duration beagle

study, animals exposed to 0.4 or 1.2 μCi ^{90}Sr/kg/day (14.8 or 44.4 kBq/kg/day) *in utero* from gestational day 21, throughout lactation, and from weaning on day 42 to day 540 exhibited only secondary hepatic effects (Dungworth et al. 1969). Livers were sometimes enlarged from myeloid infiltration and periacinar lipidosis, sometimes with terminal necrosis, in dogs with severe anemia. Since the observed myeloid infilitration was a secondary effect resulting from irradiation of the bone marrow, it is not categorized under Systemic: Hepatic Effects in Table 3-3.

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to radioactive strontium isotopes. Approximately 19% of adult Long-Evans rats ingesting 65 μCi ^{90}Sr/day (2.41 MBq/day; 135 or 194 μCi/kg/day, 5 or 7.2 MBq/kg/day for males and females, respectively) of in drinking water for 10 days developed chronic interstitial nephritis, a common disease in older rats, during their remaining lifespan (Casarett et al. 1962). It is very unlikely that the ingestion of radiostrontium was related to the occurrence of nephritis.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to radioactive strontium isotopes.

No studies were located regarding ocular effects in animals after acute- or intermediate-duration oral exposure to radioactive strontium isotopes. In one chronic-duration study, 2 out of 403 beagles that had been exposed to ^{90}Sr *in utero* from gestational day 21, during lactation, and from weaning on day 42 to day 540, developed a benign melanoma of the eye, but the dose-level was not reported (Raabe et al. 1994). Statistical analysis showed that these tumors (not found in controls, but also found in dogs irradiated through other exposure routes, or with other radionuclides) were significantly related to exposure to ionizing radiation. According to a 6-year report from the same chronic-duration beagle study, animals exposed to 0.4 or 1.2 μCi ^{90}Sr/kg/day (14.8 or 44.4 kBq/kg/day) *in utero* from gestational day 21, throughout lactation, and from weaning on day 42 to day 540 exhibited only indirect ocular effects (Dungworth et al. 1969). The eyes of dogs with a myeloproliferative disorder exhibited some slight degree of myeloid infiltration (see Section 3.3.2.7 Cancer). Since this was a secondary effect resulting from irradiation of bone marrow and not the direct response of the eye tissues to radiostrontium, it is not categorized under Ocular Effects in Table 3-3.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to radioactive strontium isotopes. No studies were located regarding body weight effects in animals after acute- or intermediate oral exposure to radioactive strontium. No effect on body weight was

observed among female CF-1 mice that had been exposed to ^{90}Sr *in utero*, during lactation, and up to day 414 at doses of up to 36 μCi of ^{90}Sr/kg/day (1.33 MBq/day) (Finkel et al. 1960). Progressive weight loss was observed among beagle dogs that developed anemia after having been exposed to 0.4–1.2 μCi of ^{90}Sr/kg/day (148–444 kBq/kg/day) from mid-gestation to age 1.5 years (Dungworth et al. 1969).

3.3.2.3 Immunological and Lymphoreticular Effects

Immunological changes were reported in the Techa River population that was exposed to chronic combined external gamma radiation and internal radiation from ^{90}Sr and ^{137}Cs between 1949 and 1956 (Akleyev et al. 1995). Immunological disorders persisted for 30 years and included decreased expression of antigens of differentiating T-lymphocytes, decreased T-lymphoblast transformation, and reduced counts of large granulocytic lymphocytes. Granulocytopenia developed in a portion of the exposed population that received radiation to the bone marrow at rates in excess of 30–50 rem (0.3–0.5 Sv) per year. Akleyev et al. (1995) suggested that radiation-induced immunodeficiency may have contributed to the higher incidence of leukemia in the exposed population (see Section 3.3.2.7 Cancer). Clinical manifestations of immune insufficiency in exposed cancer patients included 3-fold increases in the incidences of infectious diseases (chronic pneumonia, chronic bronchitis, pulmonary tuberculosis, and osteomyelitis) compared to a nontumor-bearing group. These data are omitted from Table 3-3 because of the mixed exposures.

No animal studies were located that described immunological effects following acute oral uptake of radiostrontium. Intermediate-to-chronic-duration exposures to radiostrontium resulted in impaired immune function in animals. In Pitman-Moore miniature pigs that were fed 625 μCi ^{90}Sr/day (23.13 MBq/day) as strontium chloride for 9 months, the antibody response to inoculated *Brucella abortus* (strain 19) antigen was determined by the plate agglutination test to be less than half that of controls (Howard 1970). In another test, peripheral leukocyte cultures were prepared from these same animals at monthly intervals, in medium containing phytohemagglutinin (PHA). In pigs that were fed 625 μCi ^{90}Sr/day (23.13 MBq/day) for 4–5 months, peripheral lymphocytes lost the ability to respond to PHA stimulation; this adverse effect was sustained for at least 6 months. The author attributed these immunological effects to exposure to ^{90}Sr. Myeloid metaplasia also afflicted female Pitman-Moore miniature swine that were fed 3,100 μCi ^{90}Sr/day (114.7 MBq/day) until the end of life at age 3–4 months (Howard and Clarke 1970). The cumulative doses at the time of death ranged from 40 to 10,000 rad (0.4–100 Gy).

In a 6-year status report of a chronic uptake study in which beagle dogs were exposed to ^{90}Sr from midgestion to age 1.5 years, 1.3% of dogs receiving 0.4 μCi ^{90}Sr/kg/day (14.8 kBq/kg/day) and 3.7% of dogs receiving 1.2 μCi ^{90}Sr/kg/day (44.4 kBq/kg/day) developed myeloid metaplasia of the spleen (Dungworth et al. 1969).

The highest reliable NOAEL values and all LOAEL values for immunological and lymphoreticular effects from oral exposure to radioactive strontium in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.3.2.4 Neurological Effects

Nervous system disorders (weakness, apathy, fatigue) were reported in the Techa River population that was chronically exposed to combined external gamma radiation and internal radiation from ^{90}Sr and ^{137}Cs (Akleyev et al. 1995). Neurological effects were observed at chronic dose rates in excess of 40–50 rad (0.4–0.5 Gy) per year and persisted for 14–20 years in the exposed population. However, it is not clear to what extent strontium-derived radiation contributed to neurological effects, compared to external gamma radiation. These data are omitted from Table 3-3 because of the mixed exposures.

No studies were located that reported neurological effects in animals following oral exposure to radioactive strontium isotopes.

3.3.2.5 Reproductive Effects

No significant reproductive effects were reported in the Techa River population that was exposed to combined external gamma radiation and internal radiation from ^{90}Sr and ^{137}Cs between 1949 and 1956 (Kossenko et al. 1994). Exposure had no effect on birth rate, fertility, or the incidence of spontaneous abortions in the study group that had received average doses to the gonads of up to 74 rem (0.74 Sv), primarily from external gamma radiation (Akleyev et al. 1995). An increase in the incidence of ectopic pregnancies was not dose-associated. These data are omitted from Table 3-3 because exposures were to multiple sources and it is probable that radiostrontium had a minor effect on the gonadal radiation dose.

In one acute study, female rats were given a single dose of 400 μCi ^{90}Sr/kg by gavage 1–10 days before impregnation (Moskalev et al. 1969). At the time of conception, the maternal skeletal dose was 800 rad

(8 Gy) and soft tissue dose was 10 rad (0.1 Gy). Fetuses received skeletal doses of 20 rad (0.2 Gy). Under these conditions, 22% of fetuses died. In an intermediate-duration study, groups of 230–339 female CF-1 mice were fed ^{90}Sr in the diet at doses between 0.03 and 31 μCi/kg/day (1.11 and 1,147 kBq/day; Finkel et al. 1960). Dams and males bred while on the radiostrontium diet, and dams were maintained on diet throughout gestation and lactation. Radiostrontium feeding had no effect on fertility, the number of live offspring, or the number of female offspring surviving at PND 35.

In a multigenerational study, 9-month-old female Pitman-Moore miniature swine were fed a diet containing between 1 and 3,100 μCi ^{90}Sr/day (0.037 and 114.7 MBq/day) and then were bred with males that were only exposed to ^{90}Sr during the period of mating (Clarke et al. 1970, 1972; McClellan et al. 1963). Ingestion of radioactive strontium had no effect on fertility or fecundity. Pregnant sows receiving 3,100 μCi ^{90}Sr/day (114.7 MBq/day) did not survive to the end of the period of gestation because of bone marrow hypoplasia, but their fetuses were apparently normal (McClellan et al. 1963). For doses between 1 and 625 μCi ^{90}Sr/day (0.037 and 23.13 MBq/day), there was no significant effect on litter size, percentage of stillborn, or birth weight. Exposure had no effect on frequency and duration of the estrus cycle or in the number of repeat breedings. However, the F1 offspring of the sows ingesting 625 μCi ^{90}Sr/day (23.13 MBq/day) did not survive to adulthood. Survival of the F2 offspring was apparently similar to the F1 generation, but their reproductive capacity was not reported, since later studies focused on cancer effects.

The highest reliable NOAEL values and all LOAEL values for reproductive effects from oral exposure to radioactive strontium in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.3.2.6 Developmental Effects

Few developmental effects were reported in the progeny of the Techa River population that was exposed to combined external gamma radiation and internal radiation from ^{90}Sr and ^{137}Cs between 1949 and 1956 (Kossenko et al. 1994). The cohort of women in the study received radiation doses to the gonads of up to 74 rem (0.74 Sv), primarily from external gamma radiation (Akleyev et al. 1995); the proportion of the dose attributable to radiostrontium was not specified, but is likely to have been relatively small. No increase in the incidences of spontaneous abortion, miscarriages, or stillbirths was observed. However, there were slight increases in child mortality from chromosomal defects and from congenital anomalies of

the nervous system, circulatory system, and other unspecified anomalies in the progeny of the exposed group compared to controls. Considering deaths from these anomalies, from labor complications, or from unspecified perinatal causes, the mortality coefficient of the offspring of parents with gonadal doses of 11 rem (0.11 Sv) was double that of the unexposed control group. Kossenko et al. (1994) calculated that the gonadal doses required to double the incidences of stillbirths, miscarriages, early neonatal mortality, or lethal developmental effects were rather high, ranging from 20 to 480 rem (0.2–4.8 Sv) for the different end points. These data are omitted from Table 3-3 because of the combined internal and external radiation exposures.

In one animal study, CF-1 mice were exposed to ^{90}Sr from the time of conception; breeding adults were fed a diet containing 0.03–31 μCi ^{90}Sr/kg/day (1.11–1,147 kBq/kg/day), and the dams were fed the same diet throughout gestation and lactation (Finkel et al. 1960). The offspring were fed the same diet throughout their lifetimes. Gestational exposure to radiostrontium did not affect litter size or early survival of offspring, and no teratogenic effects were noted. However, survival of the offspring was shortened at doses of 3 μCi ^{90}Sr/kg/day (111 kBq/kg/day) or higher, which was related to the higher incidence of bone-related cancer (see Section 3.3.2.7 Cancer). Autoradiographs demonstrated the uniform distribution of ^{90}Sr in the skeleton, which probably contributed to these effects.

In a large multigenerational study, 9-month-old female Pitman-Moore miniature swine were fed a diet containing between 1 and 3,100 μCi ^{90}Sr/day (0.037 and 114.7 MBq/day) and then were bred with males that were only exposed to ^{90}Sr during the period of mating (Clarke et al. 1970, 1972; McClellan et al. 1963). Ingestion of radioactive strontium had no effect on fertility or fecundity. Fetuses were apparently unaffected, even those of sows that died during pregnancy from bone marrow hypoplasia after ingesting 3,100 μCi ^{90}Sr/day (114.7 MBq/day; McClellan et al. 1963). For doses between 1 and 625 μCi ^{90}Sr/day (0.037 and 23.13 MBq/day), there was no significant effect on litter size, percentage of stillborn, or birth weight. In offspring of sows ingesting 625 μCi ^{90}Sr/day (23.13 MBq/day), the weaning weight was reduced because radiation-induced hematopoietic effects reduced the output of milk (Clarke et al. 1970). After weaning, the F1 offspring were fed ^{90}Sr in the diet at graded levels that, by 6 months, equaled the maternal level, 1–625 μCi ^{90}Sr/day (0.037–23.13 MBq/day). The 625 μCi ^{90}Sr/day (23.13 MBq/day) F1 females did not survive to be bred at 9 months. These results indicate an age-related vulnerability to ^{90}Sr, since the 625 μCi ^{90}Sr/day (23.13 MBq/day) dosage was not lethal to the parental generation (pigs exposed from age 9 months).

The highest reliable NOAEL values and all LOAEL values for developmental effects from oral exposure to radioactive strontium in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.3.2.7 Cancer

Epidemiological studies have found little or no association between oral exposure to radioactive strontium from fallout and cancer effects in humans. In an epidemiological study using the Danish cancer registry, no association was found between the incidence of thyroid cancer in Denmark between 1943 and 1988 and the levels of skeletal incorporation of ^{90}Sr from fallout (Sala and Olsen 1993). In another epidemiological study, data collected between 1959 and 1970 in a ^{90}Sr monitoring program in Glasgow, Scotland, were used to identify three cohorts with respect to the hypothetical risk for leukemia and non-Hodgkin's lymphoma, acute myeloid leukemia, all childhood cancers combined, and bone tumors (Hole et al. 1993). The three cohorts were a high risk group born in 1963–1966 (exposed to high levels of fallout, i.e., ^{90}Sr, at a young age), a medium risk group born in 1959–1962 (exposed to high levels at an older age), and a low risk group born after 1966. Cumulative incidences for all cancers, leukemia and non-Hodgkin's lymphoma, and acute myeloid leukemia all showed a secular (progressive, noncyclical) increasing trend for children born before 1982. However, the study found no evidence for increased risks of total cancers, leukemia and Non-Hodgkin's lymphoma, or acute myeloid leukemia for cohorts born during the period of highest fallout (radiostrontium) exposure. The few cases of bone tumors showed a statistically nonsignificant increase for children born during the 'high risk' period.

In contrast, the Techa River population that was exposed to contaminated water and food as a result of releases from a nuclear weapons facility exhibited a significant increase in the incidence of leukemia (Kossenko 1996; Kossenko et al. 1997, 2000, 2002). An excess of leukemia cases (0.85 excess cases per 10,000 person-year Gy (95% CI: 0.2; 1.5) was observed in groups of individuals with estimated bone marrow doses in excess of 10 rem (0.1 Sv), and the risk of mortality from leukemia increased with increasing dose (Kossenko, 1997, 2002). This finding can be related to the body burdens of ^{90}Sr, which in the Techa River cohort, have been >100 times higher than fallout-related exposures during the same period (Shagina et al. 2000). No increase in cancer rates has been observed in the progeny of the Techa River cohort (Kossenko 1996).

As shown in numerous animal studies, oral exposure to radioactive strontium may increase the incidence of cancers of bone and bone marrow. In a small study in which young monkeys were given ^{90}Sr by gavage, one given 11.2 µCi ^{90}Sr/kg/day (0.42 MBq/kg/day) for 5 days died of leukemia, with a final skeletal dose of 4,300 rad (43 Gy) 4 years after treatment (Casarett et al. 1962). Two others exposed to an average of 18 µCi ^{90}Sr/kg/day (0.67 MBq/kg/day) for 10 days died from bone-associated cancers (chondrosarcoma, osteosarcoma) within 36 months of treatment, with estimated skeletal doses of 4,700–9,500 rad (47–95 Gy).

Acute-duration experiments using Long-Evans rats demonstrated that weanlings, with their relatively higher rate of incorporation of strontium into the skeleton, were more vulnerable than adults to the carcinogenetic effects of ^{90}Sr (Casarett et al. 1962). Weanlings (30 days old) were given 46 µCi ^{90}Sr/day (1.7 MBq/day) and adults were given 33 or 65 µCi ^{90}Sr/day (1.2 or 2.4 MBq/day) in drinking water for 10 days; on a body weight basis, the amounts given were >300 µCi/kg/day (11 MBq/kg/day) for weanlings, 64 or 135 µCi/kg/day for adult males, or 92 or 194 µCi/kg/day for adult females. After 5 months, 33 µCi (1.2 MBq) of radioisotope were detected in the skeletons of weanlings that received 460 µCi (17 MBq), but only 1 or 2 µCi (37 or 74 kBq) were detected in the skeletons of adults that received 330 or 650 µCi (12.2 or 24.1 MBq), respectively. The differences in incorporation of ^{90}Sr probably accounted for the age-related differences in the incidence of osteosarcoma; 17.5% of weanlings developed osteosarcoma compared to none of the adults. However, in the high dose adults, the overall incidence of malignancy (leukemia, squamous cell carcinoma of the skin, various other carcinomas) was more than doubled, compared to controls. At the lower dose, the overall rate of malignancies in adults was lower than in controls (6.25% compared to 16.2%). In an intermediate-duration experiment, in which male 87-day-old Long-Evans rats were given 74 µCi ^{90}Sr/kg/day (2.7 MBq/kg/day) and females were given 104 µCi ^{90}Sr/kg/day (3.8 MBq/kg/day) in drinking water for 30 days (total 790 µCi; 29.2 MBq), the incidence of osteosarcomas was 27.5% compared to none in the controls. Overall, the incidence of malignancy in the treated group was more than double that of controls; other neoplasms included 11.25% skin carcinoma (facial) and 6.25% leukemia. The 87-day-old rats treated for 30 days had a 5-month skeletal burden of about 11µCi (407 kBq), which, on a kg body weight basis, was less than one quarter that of weanlings treated for 10 days. This discrepancy reflects differences in rates of absorption and osteogenesis, which are higher in the younger rats. The older rats had a higher incidence of osteosarcoma than the weanlings because they survived beyond the latency period for the cancer. In another intermediate-duration rat study, oral exposure to ^{90}Sr for 37 days (total dose of 790 µCi; 29.2 MBq) increased the incidence of osteolysis and osteogenic sarcoma by 21% (Hopkins et al. 1966). The radiation dose to the skeleton after 150 days was 4,000 rad (40 Gy). Young rabbits (~52 days old) that

were fed an average of 6 μCi ^{90}Sr/kg/day (218 kBq/kg/day) ^{90}Sr in pellets for 224–280 days developed multiple osteogenic sarcomas in the skull and at the rapidly growing ends of the long bones within 6–8 months (Downie et al. 1959).

Relatively large studies in rats, mice, dogs, and pigs demonstrated increased tumor induction following chronic ingestion of ^{90}Sr. In the rat study, albino rats were fed between 0.05 and 2 μCi ^{90}Sr/kg/day for their post-weaning lifetime, resulting in exposures between 0.01 and 0.4 μCi/day (Zapol'skaya et al. 1974). In rats consuming 2 μCi ^{90}Sr/kg/day, the number of rats with malignant tumors was 18.7%, compared to 1.3% for controls. At 0.5 ^{90}Sr/kg/day, the tumor incidence was 3–6 times lower (not specified numerically), but the outcome at 0.05 ^{90}Sr/kg/day was not reported. The most common malignancies were lymphosarcoma (8%), osteosarcoma (6.7%), and "leukosis" (4%). The latency periods were 300–540 days for lymphosarcomas and 450–660 days for "leukosis" and osteosarcoma. The cumulative absorbed doses averaged 1,350 rad (13.5 Gy) just before the onset of lymphosarcoma, 2,200 rad (22 Gy) just before the onset of 'leukosis', and 2,400 rad (24 Gy) just before the onset of osteosarcoma.

In the mouse study, mice were exposed either as adults (beginning at age 110–250 days) or from conception to 0.05–36 μCi ^{90}Sr/kg/day (Finkel et al. 1960). There was a higher incidence of reticular tumors in blood-forming tissues, but no evidence of osteogenic sarcoma in all adult exposed groups. Possibly because of the experimental design-groups were not exposed simultaneously and were subjected to environmental differences-tumor incidence in adults did not show a clear dose-response. However, the tumor incidence was significantly elevated in mice exposed to ^{90}Sr from conception. The highest dose level resulted in the early appearance of reticular tumors, especially lymphomas; 24% of mice at this level died with reticular-tissue tumors by 525 days, compared to 6% in controls. Other tumors unique to the high-dose level included six osteogenic sarcomas, four osteolytic tumors, and two epidermoid carcinomas of the oral cavity. Radiography demonstrated that radioactive strontium was ubiquitously distributed throughout the skeleton of mice exposed from conception.

In the dog study, groups of pregnant beagles were fed between 0.002 and 3.6 μCi ^{90}Sr/kg/day (0.074 and 133.2 kBq/kg/day) from day 21 of gestation to postnatal day 42 (White et al. 1993). The pups were weaned and then fed a diet containing the same ^{90}Sr/calcium ratio as the dam until day 540. Bone sarcoma deaths occurred in dogs ingesting between 0.13 and 3.6 μCi ^{90}Sr/kg/day (4.8–133.2 kBq/kg/day) resulting in bone doses at death of 5,000–10,700 rad (50–107 Gy), but not at 0.002–0.043 μCi ^{90}Sr/kg/day (0.1–1.6 kBq/kg/day) with doses to death of 100–2,300 rad (1–23 Gy). The higher the amount of ^{90}Sr

given, the earlier the age of onset of sarcomas and the more likely they were to be osteosarcomas. Of 66 sarcomas, 75% were osteosarcomas; other types were chondrosarcoma, hemangiosarcoma, fibrosarcoma, and undifferentiated sarcoma. Multiple tumors occurred only at the two highest doses. Other cancer deaths occurred at high doses: radiation-induced myeloid leukemia (43 deaths), oral or nasal carcinoma (29 deaths), and periodontal carcinoma (16 deaths). The leukemic animals (average age at death 1,156 days) were not at risk for osteosarcoma, which had an average age of onset of 2,864 days. The mean cumulative skeletal doses at the time of onset in the four highest exposure groups for dogs with tumors were between 3,100 and 11,600 rad (31–116 Gy). The authors indicated that of the exposures that did not give rise to tumors, the lowest exposure (8 mrad/day; 0.08 mGy/day) was 25 times higher than background and the highest (146 mrad/day; 1.46 mGy/day) was 500 times higher than background. Therefore, lifetime chronic exposure to low linear energy transfer (LET) beta particle radiation up to 500 times background showed no apparent carcinogenic potential in dogs.

Stage-specific differences in carcinogenetic effects were reported in a large multigenerational study of female Pitman-Moore miniature swine that were fed between 1 and 3,100 μCi ^{90}Sr/day (0.037–114.7 MBq/day) for life (Clarke et al. 1972; Howard 1970; Howard and Clarke 1970). In the parental generation, which was started on the regimen at age 9 months of age, myeloid metaplasia was observed at nearly all levels, and lymphoid or myeloid neoplasms were observed when between 1 and 125 μCi ^{90}Sr/day were ingested. The average doses to the skeleton for the parental females were between 40 and 10,000 rad. No bone cancer occurred in the parental generation, whereas osteosarcomas occurred in F1 or F2 offspring exposed from conception to 125 or 625 μCi/day with average skeletal doses higher than 9,000 rad (90 Gy). Osteosarcoma had a longer latency period and occurred at higher exposure levels. Myeloid metaplasia and myeloid and lymphoid neoplasms developed sooner and more frequently in the F1 and F2 generations than in the parental generation.

The cancer effect levels (CELs) resulting from oral exposure to radioactive strontium in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.3.3 External Exposure

Cardiovascular, dermal, ocular, and cancer effects have been reported following acute- or intermediate-duration external exposure to beta radiation from a solid radioactive strontium source apposed to the skin or eye. In these studies, ^{90}Sr was considered to be in equilibrium with ^{90}Y; that is, following decay of ^{90}Sr, some radiation emissions could be expected from decay of its transformation product, ^{90}Y.

3.3.3.1 Death

No studies were located regarding death in humans or animals after external exposure to radioactive strontium.

3.3.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or endocrine effects in humans or animals after external exposure to radioactive strontium isotopes.

Cardiovascular Effects. Exposure to excessive ionizing radiation is known to affect the integrity of the vasculature of the skin, increasing the permeability of the vasculature to plasma protein. A study by Song et al. (1968) examined the ability of several anti-inflammatory agents to suppress this radiation-induced increase in vascular permeability. Albino male guinea pigs were exposed to 3,000 rep (Roentgen equivalent, physical) (3,230 rad; 1 rep≈0.93 rad) of particles (800 rad/min; 8.0 Gy/min) from a $^{90}Sr/^{90}Y$ source. Immediately after irradiation, ^{125}I-labeled guinea pig serum albumin was injected into the heart as a tracer. The peak increase in vascular permeability, as measured by the ratio of accumulation of labeled plasma protein in the nonirradiated control and beta-irradiated skin, was determined to occur at 18 hours. In the group receiving no anti-inflammatory drug, the irradiated epidermis and dermis exhibited approximately 3- and 1.6-fold increases in the peak accumulation of plasma protein, respectively.

The highest reliable NOAEL values and all LOAEL values for cardiovascular effects from external exposure to radioactive strontium in each species and duration category are recorded in Table 3-4.

Dermal Effects. Several studies in humans and animals have reported damage to the skin following external exposure to radioactive strontium. Beta radiation from ^{90}strontium has been used to treat hemangiomas in children and adults. One study described some delayed effects of this radiation treatment within patients in one medical practice in Belgrad, Yugoslavia (now Serbia; Bekerus 1970). The beta source was a 50 mCi ^{90}Sr plate with a diameter of 9.9 mm. Adults were treated with an initial dose of 1,600 rad (16 Gy) and subsequent doses of 1,080–1,600 rad (10.8–16 Gy) in succeeding months,

Table 3-4 Levels of Significant Exposure to Strontium - Radiation Toxicity - External Radiation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
ACUTE EXPOSURE							
Systemic							
1	Human	once <1 min	Ocular		1700 (scleral thinning in diabetic patient)		Wesberry and Wesberry 1993 Strontium-90
2	Mouse (SAS/4)	1-60 min once	Dermal		2200 M (50% incr moist desquamation)		Hopewell et al. 1986 Strontium-90/yttrium-90
3	Mouse (ICR)	9 min once	Dermal			2700 F (acute injury, scarring)	Hoshino and Tanooka 1975 Strontium-90/yttrium-90
4	Mouse (CD-1)	once	Dermal			5000 M (late chronic fibrosis)	Randall and Coggle 1995 Strontium-90/yttrium-90
5	Mouse (CBA/ca agouti)	once	Dermal			5000 M (late chronic fibrosis)	Randall and Coggle 1995 Strontium-90/yttrium-90

Table 3-4 Levels of Significant Exposure to Strontium - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
6	Gn Pig (albino)	1.4 to 8.3 min once	Dermal		1000 M (reversible 25% loss of basal cells; erythema; hair loss)		Etoh et al. 1977 Strontium-90/yttrium-90
7	Gn Pig (albino)	4 min once	Cardio		3230 M (incr vascular permeability in dermis)		Song et al. 1968 Strontium-90/yttrium-90
8	Pig (Large White)	1-60 min once	Dermal			2000 F (late 35% dermal atrophy)	Hamlet et al. 1986 Strontium-90/yttrium-90
9	Pig Large White	once 3 to 12 min	Dermal		2340 F (moist desquamation)		Hopewell et al. 1985 Strontium-90
10	Pig (Large White)	1-60 min once	Dermal		3000 F (50% incr moist desquamation)		Hopewell et al. 1986 Strontium-90/yttrium-90

Table 3-4 Levels of Significant Exposure to Strontium - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL				Reference Chemical Form
					Less Serious (rad)		Serious (rad)		
11	Pig (Large White)	1-60 min once	Dermal		3000 F	(50% incr moist desquamation)			Peel et al. 1984. Strontium-90/yttrium-90
	Cancer								
12	Mouse (ICR)	1 hr once					17800 F	(CEL: 1/5 fibrosarcoma of skin)	Hoshino and Tanooka 1975 Strontium-90/yttrium-90
	INTERMEDIATE EXPOSURE								
	Systemic								
13	Human	1 yr ~1 x/mo ~min/d	Dermal		220	(delayed telangiectasis, slight atrophy)			Bekerus 1970 Strontium-90

Table 3-4 Levels of Significant Exposure to Strontium - Radiation Toxicity - External Radiation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (rad)	LOAEL Less Serious (rad)	LOAEL Serious (rad)	Reference Chemical Form
14	Human	3 wk 1 x/wk <1 min/d	Ocular		1075 (conjunctival telangiectasis, scarring; abnormal nuclei of conjunctival epithelium)		Tong et al. 1969 Strontium-90
	Cancer						
15	Mouse (ICR)	43 wks 1 x/wk 1 hr				17800 F (CEL: 1/5 reticulocyte sarcoma)	Hoshino and Tanooka 1975 Strontium-90/yttrium-90
16	Mouse (ICR)	177-300 d 3 x/wk ~min/d				150 F (CEL: fibrosarcoma; squamous cell carcinoma; basal cell carcinoma)	Ootsuyama and Tanooka 1988 Strontium-90/yttrium-90
17	Mouse (ICR)	177-300 d 3 x/wk ~min/d				150 F (CEL: osteosarcoma)	Ootsuyama and Tanooka 1989 Strontium-90/yttrium-90

[a] There is no corresponding LSE figure.

1 In these studies, a solid radioactive source was placed adjacent to the eye or skin.

~ = approximately; CEL = cancer effect level; d = day(s); Gn pig = guinea pig; hr = hour(s); incr = increased; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level

not exceeding a total of 7,530 rad (75.3 Gy). Children were treated with an initial dose of 200–300 rad (2–3 Gy) and additional treatments over 6–16 months, for a total exposure of 2,420–6,130 rad (24.2–61.3 Gy) in some cases. Eight or 10 years after treatment, about a third of the patients developed delayed reactions to radiation: achromia, excess pigmentation, slight atrophy, and telangiectasis. The author did not specify the exposure levels that resulted in these effects.

Acute dermal reactions to ^{90}Sr have been described for depilated skin in mice, guinea pigs, and pigs. In mice, skin exposed to a single 2,000–5,000 rad (20–50 Gy) dose of beta radiation from a ^{90}Sr-^{90}Y source sustained an acute reaction (Hoshino and Tanooka 1975; Randall and Coggle 1995). For example, all mice exposed once to 5,000 rad (50 Gy) from a 1 mm diameter source developed an acute skin reaction with the following characteristics (Randall and Coggle 1995). After an asymptomatic period of 3 or 4 days, the skin exhibited increasing erythema and pigmentation changes, leading to dry desquamation by day 10. Within a few days, exposed skin entered a period of moist desquamation, during which a serum scab was formed that was prevalent between days 15 and 25. Re-growth of the epithelium commenced at the edges of the irradiated field and from surviving hair follicles. By 1 month postirradiation, the epidermis was overtly normal, although histologically hyperplastic. Chronic fibrosis was a delayed skin reaction that was not apparent until 3–6 months postirradiation.

Dose-related effects were noted in guinea pig skin that was treated with a 25x25 mm square ^{90}Sr source (Etoh et al. 1977). At 1,000 rad, there was a transient 25% reduction in the number of basal epithelial cells by day 10, which approached normality by day 15. At 2,200 rad, the epithelial basal cell population dropped by about 60% at day 12, but was slightly above normal by day 20. At 3,000 and 5,000 rad, the basal epithelial cell population was reduced 75%, but hyperplasia was also detected at the margin of the field. Hyperplasia was maintained for the 50-day observation period following exposure to 2,200–5,000 rad. At 3,000 rad, erythema was noted by day 14, followed by dry desquamation and complete hair loss by day 21. A similar pattern, with ulceration at 1 month, was seen at 5,000 rad.

Within certain ranges, field-size effects for acute, localized external exposures to radioactive strontium have been demonstrated in mice and pigs. Hopewell et al. (1986) exposed young SAS/4 male mice to different levels of radiation from ^{90}Sr sources varying in diameter between 1 and 22.5 mm. 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. Acute tissue breakdown was only achieved in mouse skin by very high doses ($ED_{50} \geq$14,000 rad) when the smallest sources were employed ($\leq$2 mm in diameter). In a parallel study in pigs, moist desquamation occurred at 2,250–7,500 rad (22.5–75 Gy) and acute tissue necrosis

occurred at doses of ≥14,000 rad (140 Gy) (Hopewell et al. 1985, 1986). Peel et al. (1984) compared the effect on pigskin of acute exposure to ^{90}Sr sources with diameters between 1 and 40 mm. The effects of acute beta radiation included epithelial cell death within the first 16 weeks, and subsequently, dermal necrosis that was attributed to vascular damage. The rate of repair was dependent on the size of the exposed area, since repair was dependent upon the migration of healthy cells into the wound. Transient moist desquamation associated with bright red erythema was observed between 4 and 6 weeks. At 'high' doses, this intensified and the dermis became ulcerated, but healed with scarring. After doses ≥4,000 rad (22.5-mm source), 6,600 rad (11-mm source), or 12,500 rad (5-mm source), a dusky red or mauve erythema followed by dermal necrosis occurred between weeks 10 and 16. In pigs that were acutely exposed to the same range of ^{90}Sr sources at the age of 3 months, dose-dependent dermal atrophy was detected in the irradiated field 2 years later, reaching a maximal 55% reduction in dermal thickness for all doses above 4,500 rad (45 Gy; Hamlet et al. 1986). Dermal atrophy was produced by doses below the threshold required to induce moist desquamation. The threshold dose for moist desquamation following irradiation by the 22.5 mm source (2,250 rad) produced a 38% thinning of the dermis. Irradiation from the 1-mm source produced 30% dermal thinning at the threshold (7,250 rad). Irradiation from the 5-mm source (2,000 rad) reduced the thickness of the dermis by 35%. For the 11–22.5-mm sources, above doses that caused maximal thinning (in the range of 12,000–6,250 rad, respectively), the relative dermal thickness increased slightly, but remained 30–40% thinner than normal.

The highest reliable NOAEL values and all LOAEL values for dermal effects from external exposure to radioactive strontium in each species and duration category are recorded in Table 3-4.

Ocular Effects. Beta radiation has been employed medically to treat pterygium, an alteration in the conjunctival connective tissue that results in the penetration of the superficial corneal stroma by vascular connective tissue (Tong et al. 1969; Wesberry and Wesberry 1993). As an adjunct to surgical removal of the pterygium, a solid ^{90}Sr source is apposed to the site in order to reduce neovascularization. Several clinical studies reported complications resulting from this procedure. Serious effects (radiation cataracts, keratinization and telangiectasis of the conjunctiva) resulted from the high dose levels used when the technique was first employed using other beta-emitting radionuclides (Merriam 1955). Atrophy of the sclera occurred after a dose of 1,600 rad from ^{90}Sr. In a later study, 78 eyes in 62 patients were treated with 1,080 rad (10.8 Gy) of beta radiation from a ^{90}Sr source repeated at weekly intervals (total dose 3,200 rad; 32 Gy; Tong et al. 1969). Because pterygia recurred within 2–18 months, six patients were re-treated as before, two were given a single dose of 2,100 rad (21 Gy), and one of these two received a third dose of 2,100 rad (21 Gy). One eye, which had received treatments of 5,380 rad (53.8 Gy) each to two

adjacent fields, developed keratitis of the cornea. Other complications noted were telangiectasis of the conjunctiva (27%), scarring of the conjunctiva (14%), and scarring of the cornea (3%); the authors did not specify the exposure levels at which these side effects occurred. A more recent study described results for 171 eyes that had been treated with single doses of 1,700–1,800 rad (17–18 Gy) (Wesberry and Wesberry 1993). During follow-up periods lasting between 1 and 19 years, the only complications noted were one case each of corneal scarring, iritis, conjunctivitis, mild irritation, and, in a diabetic patient, scleral thinning. A complication rate of 1.8% was reported for a study of 490 eyes (399 patients) that received doses between 31 and 42 Gy (3,100–4,200 rad) in four or five fractions over 29 days (Nishimura et al. 2000). Scleral thinning, not severe enough to require treatment, was reported for four eyes in three patients 0.5, 2, and 9 years after treatment. Infectious scleral ulcer occurred within weeks of treatment in one male. Ischemic necrosis of the sclera in one male and adhesion of the eyelid and eyeball in one female occurred several years after repeat treatments for recurring pterygia; adhesive scarring of the eyelid occurred in one female 7 years after treatment.

No studies were located regarding ocular effects in animals after external exposure to radioactive strontium isotopes.

The highest reliable NOAEL values and all LOAEL values for ocular effects in humans from external exposure to radioactive strontium in each duration category are recorded in Table 3-4.

No studies were located regarding the following effects in humans or animals after external exposure to radioactive strontium isotopes:

3.3.3.3 Immunological and Lymphoreticular Effects

3.3.3.4 Neurological Effects

3.3.3.5 Reproductive Effects

3.3.3.6 Developmental Effects

3.3.3.7 Cancer

Development of skin cancers in mice following localized exposure to beta radiation from a solid ^{90}Sr-^{90}Y source depended on the dose and on strain susceptibilities (Hoshino and Tanooka 1975). In experiments

using a 40 mCi ($1.48x10^9$ Bq) ^{90}Sr-^{90}Y source that delivered doses of 290 rad/min (2.9 Gy/min) to the skin, ICR mice exposed to a single localized dose of 2,700 rad (27 Gy) developed an acute skin reaction within the first month (see Section 3.3.4.2 Dermal Effects), but did not develop skin cancer during a 23-month observation period (Hoshino and Tanooka 1975). When the exposure was repeated 7 times for a total dose of 17,800 rad (178 Gy), one fibrosarcoma of the skin appeared after 10 months among five mice. Even extending the duration of the repeated 17,800 rad treatment for 43 weeks did not increase the incidence of malignant skin tumor; a single reticulocyte sarcoma developed in one out of five mice. Mice from a different strain, Japanese ddN, exposed to single doses of up to 17,400 rad (174 Gy) did not develop skin tumors during a 1-year observation period (Hoshino and Tanooka 1975). In the acute dermal toxicity experiments described above, Randall and Coggle (1995) selected the exposure level of 5,000 rad (50 Gy) for their mouse studies since it is known to be a critical dose for carcinogenetic effects in humans exposed to ionizing radiation.

Ootsuyama and Tanooka (1988, 1989) exposed the backs of female ICR mice to beta radiation from a 40,000 μCi (1,500 MBq) source of ^{90}Sr–^{90}Y, which delivered a surface dose rate of 228 rad/minute (2.28 Gy/minute) and a 20–80% lower dose rate to the top of the vertebrae. Mice were irradiated 3 times weekly at skin entrance doses per exposure of 135–1,180 rad (1.35–11.8 Gy), and irradiation was continued until a palpable tumor appeared (up to 86 weeks). Tumors arising included squamous cell carcinomas, basal cell carcinomas, fibrosarcomas, and osteosarcomas. No skin tumors arose in mice receiving 135 rad/day (1.35 Gy/day). The total number of irradiations (and total dose) needed to induce 50% incidence of skin tumors ranged from 252 sessions for a total of 37,800 rad (378 Gy) for the 150 rad/day level and 156 sessions for a total of 192,300 rad (1,923 Gy) for the 1,180 rad/day level. Osteosarcomas were induced at lower doses, most frequently with skin surface doses of 250–350 rad (2.5–3.5 Gy) per exposure. In time, 100% of mice developed tumors in groups receiving 250–1,180 rad per exposure. Ootsuyama and Tanooka (1988) suggested that the 135 rad/day dose might represent a threshold dose, since no tumors formed. However, in their experimental design, they arbitrarily terminated exposures at this dose level on day 300, which conceivably could be shorter than the latency period for tumor development at that dose.

The CELs resulting from external exposure to radioactive strontium in each species and duration category are recorded in Table 3-4.

3.3.4 Other Routes of Exposure

This section includes injection and *in vitro* studies that provide evidence for the biological basis of toxicity of stable and radioactive strontium in humans and animals. Since these studies are not directly relevant to general population exposure conditions, no LSE tables have been created for this section.

Hematological Effects Hematological effects have been observed in several clinical studies in which ^{89}Sr, one of the shorter-lived radioactive isotopes of strontium, has been used in cancer therapy for the relief of pain by irradiating and destroying tumors that have metastasized to the bone marrow (Baziotis et al. 1998; Ben-Josef et al. 1995b; Blake et al. 1987c; Breen et al. 1992; Kan 1995; Lee et al. 1996; Piffanelli et al. 2001; Sciuto et al. 2001). Significant reductions in platelet and white blood cell counts (averaging 70 and 30%, respectively) were seen 3 months after patients were injected with a single therapeutic dose (40 μCi ^{89}Sr/kg; 1.5 MBq/kg) (Lee et al. 1996). In two patients who received two doses of 60 μCi ^{89}Sr/kg (2.2 MBq/kg) 6 months apart, platelet counts were significantly reduced (>30%) for at least 1 year. Similar effects have been observed in animals. Hypoplasia of the bone marrow has been observed in mice injected with ^{90}Sr (Ito et al. 1976; Nilsson 1970) or ^{89}Sr, the latter of which has been used intentionally to create mice with aplastic bone marrow (Bennett et al. 1976; Haller and Wigzell 1977; Levy et al. 1981; Merluzzi et al. 1978; Oghiso et al. 1988; Sawyer et al. 1982). CBA/J mice injected with fixed doses of ^{89}Sr that differed in the specific activity of the preparation, showed quantitative differences in the degree of bone marrow suppression (Shibata et al. 1985). Acute hematological symptoms (depression of hemopoiesis leading to anemia or hemorrhage) were observed in beagles beginning several weeks after injection of 64 or 98 μCi ^{90}Sr/kg (Dougherty et al. 1972). Transient neutropenia occurred at the 10.8 μCi ^{90}Sr/kg level, and prolonged (36-month) depression of all types of leukocytes was reported at 32.7–98 μCi ^{90}Sr/kg. No hematological effects were noted at levels between 0.57 and 3.46 μCi ^{90}Sr/kg.

Musculoskeletal Effects. Osteonecrosis was reported after 2 days for 2-day-old rats that were injected intraperitoneally with 2 mCi ^{90}Sr/kg of body weight (Hopkins and Casarett 1972). In weanling rabbits, injection of 600 μCi ^{90}Sr/kg resulted in increasing cell death of differentiating odontoblasts and pulp cells of immature teeth and disordered tooth structure (Rushton 1963). Mature teeth in the same animal, or teeth in adults injected at the age of 3 years or older, were not affected as severely.

Immunological and Lymphoreticular Effects. Evidence from injection studies in animals corroborates the sensitivity of the immune system to radioactive strontium. In mice that have been

injected with ^{89}Sr or ^{90}Sr to deplete bone marrow, NK cells are preferentially eliminated (Emmanuel et al. 1981; Gidlund et al. 1990; Haller and Wigzell 1977; Wiltrout et al. 1989). The loss of this cell population results in a reduced ability to defend against lymphoid tumors (Haller and Wigzell 1977; Luevano et al. 1981) or a transplanted methylcholanthrene-induced sarcoma (Scuderi and Rosse 1981b). In CBA/SU mice injected with $^{90}Sr(NO_3)_2$, the responsiveness of spleen cells to activation by B-cell mitogen lipopolysaccharide was reduced, which was attributed to the cytotoxic effect of ^{90}Sr on bone marrow, a source of precursor cells for the spleen (Bierke 1990). In mice injected with 400–800 μCi ^{90}Sr/kg to deplete bone marrow, the thymus went through two phases of weight loss and regeneration within 50 days (Järplid 1973).

Reproductive Effects. Numerous animal studies demonstrated adverse reproductive effects of injected radioactive strontium. For the first 4 weeks after male CBA mice were injected intraperitoneally with 18 μCi of ^{90}Sr and mated with untreated females, fetal deaths were 5–10% higher than controls (Lüning et al. 1963a). The increase in fetal mortality was much less (only ~2%) when the same males were mated 11–15 weeks postinjection (Lüning et al. 1963b). In a similar study using male C_3H/He mice, a single injection of 1,160 μCi $^{90}SrCl_2$/kg resulted in fetal death rates 7–8% higher than normal for matings conducted 10–40 weeks after injection (Reddi 1971). Autoradiography demonstrated that ^{90}Sr selectively accumulated in testicular stem cells.

When female CBA mice were injected with $^{90}Sr(NO_3)_2$ on the 19th day of pregnancy, a dose of ≥43 μCi $^{90}Sr(NO_3)_2$/kg (≥1,600 kBq/kg) transiently suppressed spermatocyte maturation of the male offspring, but the spermatid numbers had recovered by day 56 (De Rooij and Rönnbäck 1989). After the recovery period, the reproductive capacity (number of litters, litter size) of male offspring at the highest dose level (86 μCi $^{90}Sr(NO_3)_2$/kg; 3,200 kBq/kg) was unaffected. No testicular effects were observed at doses of 11 or 21 μCi $^{90}Sr(NO_3)_2$/kg (400 or 800 kBq/kg). Compared to the effect on male offspring, reproductive effects were more severe in female offspring of dams exposed to $^{90}Sr(NO_3)_2$ on the 19th day of pregnancy (Rönnbäck 1980). Dose-related decreases in the number of differentiating oocytes in the ovary were observed up to day 84 at all dose levels ranging from 5.5 to 43 μCi $^{90}Sr(NO_3)_2$/kg (200–1,600 kBq/kg). Injection on the 16–19th day was found to have more severe effects than injection earlier in gestation (Nilsson and Henricson 1969; Rönnbäck 1979). A longer-term study demonstrated that the radioactive-strontium-induced decrease in the number of oocytes in the ovary persisted for at least 10 months (Rönnbäck 1981b). Furthermore, the reproductive capacity (number of fertile females, number of litters, number of young per litter) of females treated *in utero* was significantly reduced at the two highest maternal dose levels (43 and 86 μCi $^{90}Sr(NO_3)_2$/kg; 1,600 and 3,200 kBq/kg). Rönnbäck (1981a) also

examined the effect of exposure via lactation using CBA mice receiving 21 μCi $^{90}Sr(NO_3)_2$/kg (800 kBq/kg). Ovarian cellularity, especially the earliest stages of oogenesis, was reduced in females exposed *in utero*, whether or not they suckled milk contaminated with ^{90}Sr. However, early stage oocyte numbers were somewhat improved by sucking uncontaminated milk. When unexposed newborn females were exposed to contaminated milk, the numbers of early stage oocytes was significantly reduced, but not as severely as in females exposed *in utero*. These studies suggest that reproductive capacity, particularly in females, may be adversely affected by gestational exposure to high levels of radioactive strontium. These levels are high compared to reported releases of ^{90}Sr from nuclear power facilities (see Table 6-1).

Developmental Effects. Injection of relatively high doses of radioactive strontium into pregnant animals resulted in severe developmental effects. A single dose of ≥764 μCi ^{90}Sr/kg into female Long-Evans rats had no effect on fetal mortality when administered on gestational day 10, but significantly increased fetal mortality when administered on gestational day 2 (Hopkins et al. 1967). In addition, there were dose-related increases in the incidence of fetuses with skeletal abnormalities (general stunting, lack of ossification, fusion of ribs, vertebral anomalies, missing tail). The incidence of micropthalmia was also significantly increased at the higher activity level (1,488 μCi ^{90}Sr/kg). The offspring of female Wistar rats injected with ≥100 μCi $^{90}Sr(NO_3)_2$ at gestational day 18 showed no gross malformations, but there was a significant increase in the incidence of meningeal and pituitary tumors (Schmahl and Kollmer 1981; Schmahl et al. 1979). This was shown to be connected with a late gestational increase in the transfer of transplacental strontium to the basioccipital and sphenoid bones of the skull. Tumor development was probably assisted by the position of the pituitary gland within the sella turcica, which resulted in the gland being irradiated from the ventral and lateral surfaces. The total radiation dose rate at that position was calculated to be between 60 and 120 rad for the lifespan of 30 months. After pregnant dogs were injected with 1 mCi of radiostrontium per kg (80–99% ^{89}Sr and 1–20% ^{90}Sr) 6 days prior to delivery, the puppies dying within 11 weeks exhibited abnormalities of the skeleton (underdevelopment of the jaws, incomplete and abnormal ossification, abnormal epiphyseal cartilage), partial atelectasis of the lungs, hyperplasia of lymph nodes and spleen, or deficient hematopoiesis (Finkel and Biskis 1969; Finkel et al. 1972). Puppies injected subcutaneously 12 days after birth showed some skull abnormalities and developed osteosarcomas. Effects on the reproductive system following *in utero* exposure to radioactive strontium are discussed in the preceding paragraphs. Cancer effects in animals exposed to radioactive strontium *in utero* are discussed in the next paragraph.

Cancer. Numerous studies in several species reported the induction of malignant tumors in response to injection of radioactive strontium (mice: Ash and Loutit 1977; Bierke and Nilsson 1990; Ito et al. 1976;

Loutit 1976; Nilsson 1971, 1972; Nilsson et al. 1980a; Reif and Triest 1982; Chinese hamsters: Benjamin et al. 1976b; Brooks et al. 1974; rabbits: Kshirsagar et al. 1965; Vaughan and Williamson 1969; mongrel dogs: Finkel and Biskis 1969; Finkel et al. 1971; beagle dogs: Lloyd et al. 1995; Taylor et al. 1966). In general, osteosarcomas and bone hemangiosarcomas developed at higher dose levels, and lymphomas and leukemias developed at lower levels. Carcinomas of soft tissues adjacent to bone also developed. The offspring of pregnant rats that were injected on gestational day 18 had a higher incidence of pituitary adenoma and meningeal sarcoma (Schmahl and Kollmer 1981; Schmahl et al. 1979). These findings were attributed to the higher incorporation of ^{90}Sr to the skull at that developmental period and to the anatomical position of the pituitary within the sella turcica, which subjected it to radiation from all but the dorsal surface. The female offspring of pregnant mice that were injected intravenously with 90Sr on gestational day 19 developed a higher incidence of tubular adenoma of the ovaries (Rönnbäck and Nilsson 1982).

3.4 GENOTOXICITY

There is little evidence for genotoxicity of stable strontium. However, radioactive strontium isotopes release ionizing radiation that, within an effective radius, is known to damage DNA (see Appendix D Section D.4.1 Radiation Effects at the Cellular Level). Summaries of *in vivo* and *in vitro* genotoxicity data are presented in Tables 3-5 and 3-6, respectively.

In Vivo Exposure

Stable Strontium. No studies were located regarding genotoxic effects in humans following exposure to stable strontium. The only *in vivo* genotoxicity study for stable strontium in animals involved acute oral exposure. Oral administration of 130 mg strontium/kg body weight as strontium chloride to Swiss albino female mice increased the incidence of chromosomal aberrations (gaps, breaks, nondisjunction, and polyploidy) in bone marrow cells 5-fold after 6 hours (Ghosh et al. 1990). Genotoxicity in male mice administered a similar dose (140 mg/kg) was only doubled, and therefore, was less severe than in females. At higher doses (440–1,400 mg/kg), the incidence of chromosomal aberrations was similar in both sexes after 6, 12, or 24 hours.

Radioactive Strontium. Human *in vivo* genotoxicity data are available from studies of the Techa River populations exposed to combined external gamma radiation and internal radiation from ^{90}Sr and ^{137}Cs between 1949 and 1956 and from studies on patients exposed to ^{89}Sr as a radiopharmaceutical. The stable

Table 3-5. Genotoxicity of Stable and Radioactive Strontium *In Vivo*

Species (test system)	End point	Results	Reference
Stable Strontium			
Strontium chloride:			
Mouse (bone marrow)	Chromosomal gaps, breaks, polyploidy, centric fusion	+	Ghosh et al. 1990
Radioactive Strontium			
^{89}Strontium chloride:			
Human (lymphocytes)	Transient increase in micronuclei	+	Watanabe et al. 1998
^{90}Strontium:			
Human (lymphocytes)	Chromosomal aberrations (rings, dicentric, tricentric)	+	Ilynskikh et al. 1999
Mouse (skin)	Unscheduled DNA synthesis	+	Ootsuyama and Tanooka 1986
Mouse (thymus, lymph nodes, bone marrow)	Aneuploidy	+	Ito et al. 1976
Chinese hamster (bone marrow)	Chromosomal breaks, exchanges, rings	+	Brooks and McClellan 1969
Miniature swine (leukocytes)	Chromosomal breaks in leukemic cells	+	Clarke et al. 1972; Howard 1970

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

Table 3-6. Genotoxicity of Stable and Radioactive Strontium *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Stable Strontium				
Strontium chloride:				
In vitro DNA synthesis reaction	Lack of fidelity in DNA synthesis	–	–	Loeb et al. 1977
Prokaryotic organisms:				
Bacillus subtilis Rec^-	Growth inhibition	–	–	Kanematsu et al. 1980
Eukaryotic cells:				
Chinese hamster ovary cells	Reduced cloning efficiency	–	–	Tan et al. 1984
Radioactive Strontium				
^{90}Strontium:				
Human (blood)	Chromosomal rings, dicentrics, acentrics		+	de Oliveira et al. 2001
	DNA damage in electrophoretic assay		+	
Human (lymphocytes)	Micronucleus formation		+	Mills et al. 1996
Human (lymphocytes)	Micronucleus formation		+	Hall and Wells 1988

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

chromosomal translocation frequency in peripheral lymphocytes was evaluated in 73 radiation-exposed individuals from the Techa River area and 39 unexposed individuals from noncontaminated areas (Bauchinger et al. 1998). The mean genomic frequency of translocations per cell in the exposed group ($12.8\pm1.5x10^{-3}$) was significantly elevated compared to unexposed controls ($5.7\pm1.0x10^{-3}$). Furthermore, the translocation frequency per cell was significantly higher in the subgroup that had been exposed to radiation as teenagers ($22\pm4.3x10^{-3}$) compared to the subgroup exposed as adults ($9.7\pm2.3x10^{-3}$).

Increased skeletal incorporation of radiostrontium in teenagers, leading to higher radiation doses to the bone marrow, probably contributed to the observed increase in translocation frequency for this subgroup. In a more recent study of the Techa River populations, there was a dose relationship between the frequency of chromosomal aberrations (dicentric, ring) in T-lymphocytes (assessed in 1994–1996) and whole body ^{90}Sr activity (detected by human radiation counter in 1993) for individuals residing in the Muslyumovo settlement (Ilyinskikh et al. 1999). The frequency of chromosomal aberrations was 3.8±0.8 for a non-exposed control group (whole-body ^{90}Sr activity <100 nCi), and 8.9±0.7, 12.9±1.2, and 18.7±1.9%, respectively, for exposed individuals with ^{90}Sr activity levels of 100–500, 500–1,000, and ≥1,000 nCi. In a few cancer patients who were injected with 3 mCi (111 MBq) of $^{89}SrCl_2$ to treat severe pain from multiple bone metastases, the number of micronuclei present in the lymphocytes tripled in the week after exposure, but declined in succeeding weeks (Watanabe et al. 1998). The authors found that the percentage of micronuclei, indicative of chromosomal damage, was equivalent to the damage observed in a separate *in vitro* experiment in which cells received a dose of 53 rad (0.53 Gy) by X-irradiation.

In a long-term feeding study, chromosomal breaks were noted in leukocytes of miniature pigs that had developed leukemia as a result of exposures of 25 µCi ^{90}Sr/day (925 kBq/day) or more for >1 year (Clarke et al. 1972; Howard 1970). Unexpected ("unscheduled") DNA synthesis was detected in the skin of female ICR mice several hours after external exposure to 10,000–30,000 rad (100–300 Gy) from a ^{90}Sr-^{90}Y disk applicator (surface dose rate 228 rad/min) (Ootsuyama and Tanooka 1986). Tritiated thymidine incorporation related to DNA repair was elevated to a greater degree in epithelial cells of the irradiated epidermis than in the dermis. This difference appeared to be intrinsic to the cell type, since thymidine incorporation in hair follicle epithelium situated at the same depth as fibroblastic dermal cells, occurred at a faster rate. The authors suggested that the somewhat slower rate of DNA repair in the dermis could contribute to the higher risk of cancer in the dermis, compared to the epidermis, following exposure to ionizing radiation.

A single intraperitoneal injection of ^{90}Sr–^{90}Y into Chinese hamsters (200–5,000 μCi/kg) resulted in an increasing number of chromosomal breaks/cell over time (between 2 and 224 days), as the cumulative radiation dose to the skeleton increased (Brooks and McClellan 1969). The number of chromosomal breaks and chromatid/isochromatid deletions per bone marrow cell increased as a function of dose rate, or as the activity of radionuclide injected per body weight. The relative number of chromatid exchanges and rings and dicentrics decreased with time after exposure, whereas the number of chromosomal exchanges increased. Abnormal chromosomal numbers were detected in the thymus, lymph nodes, and bone marrow of female ICR/JCL mice as late as 90 days after interperitoneal injection with 1 mCi/kg of ^{90}Sr (Ito et al. 1976).

In Vitro Exposure

Stable Strontium. In mutagenicity assays using the Rec^- (recombination-repair-deficient) strain of *Bacillus subtilis*, strontium chloride had a negative effect *in vitro* (Kanematsu et al. 1980). Furthermore, in a survey of the effect of metal salts, strontium was found to have no adverse effect on the fidelity of DNA synthesis *in vitro*, which was thought to be consistent with its reported lack of mutagenicity and carcinogenicity (Loeb et al. 1977).

The only stable strontium compound known to be genotoxic is strontium chromate. Strontium chromate induced sister chromatid exchanges in Chinese hamster ovary cells *in vitro* (Venier et al. 1985). In the Ames test using the *Salmonella typhimurium* strain TA100, strontium chromate induced mutations in the presence, but not in the absence of S9 microsomes. The genotoxicity of strontium chromate is related to the ability of the hexavalent chromium ion to enter cells and become metabolized, forming a reactive DNA-adduct. Strontium only contributes to the solubility of the salt (Elias et al. 1989, 1991).

Radioactive Strontium. Radioactive strontium has been shown to be genotoxic to human cells *in vitro*. In lymphocytes from freshly-drawn human blood, doses of 0.2–5.0 Gy (0.002–0.05 rad) increased the frequency of chromosomal aberrations (de Oliveira et al. 2001). Acentric aberrations (acentrics and double minutes) increased at ≥0.2 Gy (0.002 rad), dicentric aberrations increased at ≥0.5 Gy (0.005 rad), and there was a slight indication that the frequency of centric rings increased at ≥3.0 Gy (0.03). In the same study, results of an electrophoretic assay (comet assay) on single exposed lymphocytes revealed that DNA damage (evaluated by visual inspection and tail moment) occurred at doses as low as 0.2 Gy (0.002 rad). The varying frequencies for the different types of chromosomal aberrations were associated with the number of DNA breaks required for their formation and whether one or more chromosomes were

involved: acentrics requiring a single break and dicentrics requiring at least two breaks on different chromosomes. Dose-related increases in micronucleus formation, predominantly derived from acentric chromosomes, were reported in human lymphocytes irradiated at doses between 0.3 and 3.0 Gy (0.003 and 0.030 rad) (Hall and Wells 1988; Mill et al. 1996).

3.5 TOXICOKINETICS

3.5.1 Absorption

3.5.1.1 Inhalation Exposure

Evidence for absorption of inhaled strontium in humans is provided by several cases of accidental exposure of workers to airborne radiostrontium (Navarro and López 1998; Petkau and Pleskach 1972; Rundo and Williams 1961). Although these cases do not provide a complete quantitative description of the absorption of inhaled strontium in humans, they demonstrate clearly that inhaled aerosols of strontium compounds (e.g., $SrCl_2$, $SrTiO_3$) can be absorbed, as indicated by the detection of radiostrontium in urine and feces.

In one case, a worker accidentally inspired an unknown quantity of $^{90}SrCl_2$ (physical form unknown) and over the subsequent 800 days, ^{90}Sr was excreted in the urine with half-times of 3.3 (52%), 17 (7%), and 347 days (18%) (Petkau and Pleskach 1972). The urinary:fecal excretion ratio was 3:1. In a second case, a worker was exposed to $^{90}SrCO_3$ (physical form unknown) with deposition within the nasal tract as well as the hands, face, and hair. The actual inhaled dose could not be determined; however, based on the excretion kinetics of ^{90}Sr over the subsequent 300 days, the reconstructed internal dose was estimated to have been approximately 300–400 nCi (11.1–14.8 kBq) (Rundo and Williams 1961). Excretion in urine occurred with half-times of 2.2 (>90%), 15, and 175 days, and the urinary:fecal excretion ratio over the first 24 days was 0.71. In a third case, two workers accidentally inhaled $^{90}SrTiO_3$ (physical form unknown), and ^{90}Sr was detected in urine over a period of 225 days (Navarro and López 1998).

Studies conducted in animals have shown that the rate of absorption depends on the chemical form of the inhaled strontium aerosol. Compounds of greater solubility are, in general, more rapidly cleared from the lung. For example, strontium is rapidly cleared from the lung after inhalation of $SrCl_2$. In dogs that received a 2–22-minute nose-only exposure to an aerosol of $^{85}SrCl_2$ (activity median aerodynamic diameter [AMAD] 1.4–2.7 μm, geometric standard deviation [GSD] 2.0), <1% of the initial lung burden remained in the lung 12 hours after the exposure; 37% of the body burden was distributed to the skeleton

within 12 hours after the exposure, and 84% was in the skeleton 4 days after the exposure (Fission Product Inhalation Project 1967a). In contrast to the relatively rapid absorption of inhaled $SrCl_2$, after exposures to strontium in particles of fused clay, absorption is much slower. In dogs that received a nose-only exposure to ^{90}Sr in fused montmorillonite clay particles (AMAD 2.2 μm, GSD 1.7), the average half-time of elimination of strontium from the lung was 490 days (Snipes et al. 1974a, 1974b). Thus, strontium compounds of lower solubility are more slowly absorbed from the lung. Support for this also comes from studies in which the rates of absorption of various compounds of strontium were compared in rats. Rats were exposed to aerosols of ^{85}Sr carbonate, phosphate, fluoride, oxide, or titanate (particle sizes and doses not specified) (Willard and Snyder 1966). Greater than 99% of the initial lung burden of ^{85}Sr was cleared from the lung 5 days after inhalation of the carbonate, phosphate, fluoride, or oxide, whereas 60% of the ^{85}Sr remained in the lung after inhalation of the more insoluble strontium titanate.

In rats exposed to airborne fly ash (sieved to have a particle diameter of distribution of 90% less than 20 μm) for 6 hours, strontium was eliminated from the lung with a half-time of 23 days (observations were made for 30 days) (Srivastava et al. 1984b). One day after the exposure, the tissue:plasma strontium concentration ratios were 0.3–0.5 in the liver, kidney, small intestine, and heart. The report of this study does not indicate whether whole-body or nose-only exposures were utilized in the study; therefore, it is not possible to know for certain how much of the absorption may have resulted from ingestion of fly ash deposited on the animals. Furthermore, given the relatively large particle size of the fly ash, it is likely that deposition in the respiratory tract was largely in the tracheobronchial and nasopharyngeal region, from which the strontium may have been cleared mechanically to the esophagus and swallowed. Nevertheless, studies in which ^{89}Sr-enriched fly ash was instilled into the trachea of rats indicate that strontium in this form was partly absorbed and appeared in plasma and other tissues within days of the exposure (Srivastava et al. 1984a).

Although intratracheal instillation does not precisely replicate inhalation exposure, these studies provide additional evidence that strontium compounds of greater solubility are absorbed more rapidly from the lung. Strontium was cleared relatively rapidly from the lungs of rats that received an intratracheal dose of $SrCl_2$ (half-times <1 day) and was eliminated from the body in the urine (4–6% of the initial body burden) and in the feces (10–18%) (Naményi et al. 1986). By contrast, in rats that received an intratracheal dose of 360–760 μg Sr as $SrTiO_3$, strontium was eliminated from the lung with half-times of 0.4 days (85%) and 130 days (15%); the long retention phase reflects the slow absorption of the insoluble $SrTiO_3$ deposited in the lung, whereas the rapid phase reflects the mechanical clearance from the tracheobronchial region (Anderson et al. 1999b).

Strontium has been shown to be absorbed from the nasopharyngeal region of the respiratory tract. In hamsters administered $^{85}SrCl_2$ (in saline solution) directly into the nasal tract, 67% of the ^{85}Sr was absorbed in 4 hours and 63% was estimated to have been absorbed directly from the nasopharynx region of the respiratory tract (Cuddihy and Ozog 1973).

3.5.1.2 Oral Exposure

The fractional absorption of ingested strontium has been estimated in healthy human subjects or hospital patients who received an oral dose of strontium chloride ($SrCl_2$) or ingested strontium in the diet (Table 3-7). Absorption was quantified in these studies from measurements of plasma strontium concentration-time profiles for ingested and intravenously injected strontium (bioavailability), or from measurements of the difference between the amount ingested and excreted in feces (balance). Collectively, the results of these studies indicate that approximately 20% (range, 11–28%) of ingested strontium is absorbed from the gastrointestinal tract. Balance measurements can be expected to yield underestimates of absorption as a result of excretion of absorbed strontium in the feces (see Section 3.5.4); nevertheless, the two methods have yielded similar estimates of absorption.

Vezzoli et al. (1998) compared the area under the plasma strontium concentration-time curves in adult males and females and found no significant difference (males, 10.6±0.6 mmol/L-minute; females, 9.3±0.6 mmol/L-minute). The subjects included groups of healthy age-matched men and women (15 males, 12 females) and groups of normocalcuric patients (29 males, 18 females) who had calcium-oxalate urinary tract stones. Although the fraction absorbed could not be estimated in this study because the area under the curve for an intravenous dose was not measured, the results suggest that there were no substantive differences in absorption between males and females. This conclusion may not be valid for physiologic states in which there is an increased demand for calcium such as pregnancy and lactation. Calcium absorption is higher in these states, and studies in animals suggest that strontium absorption may also be higher (Kostial et al. 1969b). In general, strontium absorption appears to be a good indicator of calcium absorption in adult humans as both elements appear to share common mechanisms of absorption (Bianchi et al. 1999; Blumsohn et al. 1994; Milsom et al. 1987; Reid et al. 1986; Sips et al. 1994) (see Section 3.6.1).

Studies conducted in infants and children indicate that approximately 15–30% of dietary strontium is absorbed, similar to estimates in adults (Alexander et al. 1974; Harrison et al. 1965; Kahn et al. 1969a;

Table 3-7. Summary of Estimates of Absorption of Ingested Strontium in Humans

Dose and media[a]	Subjects (N)[b]	Absorption (% of dose)[c]	Comment	Reference
Tracer	Adults (9M)	28±3	Healthy adults. Absorption estimate based on whole body retention (R): R_{oral}/R_{iv}.	Likhtarev et al. 1975
44 mg, $SrCl_2$	Adults (8M)	25±7	Healthy, fasted subjects adults. Absorption estimate based on plasma AUC_{oral}/AUC_{iv}.[d]	Sips et al. 1995
44 mg, $SrCl_2$	Adults (8M)	25±6	Healthy fasted subjects. Absorption estimate based on plasma AUC_{oral}/AUC_{i}.	Sips et al. 1996
88 mg, $SrCl_2$	Adults (8M)	19±5	Healthy subjects. Dose administered with meal. Absorption estimate based on plasma AUC_{oral}/AUC_{iv}.	Sips et al. 1996
219 mg, $SrCl_2$	Adults (6M, 11F)	20	Patients with osteoporosis or chronic renal failure. Dose administered with meal. Absorption estimate based on plasma AUC_{oral}/AUC_{iv}.	Blumsohn et al. 1994
Tracer	Adults (3M)	21 (18–24)	Patients with osteoporosis. Dose administered with meal. Absorption estimate based on plasma AUC_{oral}/AUC_{iv}.	Hart and Spencer 1967
1.45 mg/kg, $SrCl_2$	Adults (6M, 4F)	22±2	Healthy fasted subjects. Absorption estimate based on fraction of dose in plasma at 3 hours.	Bianchi et al. 1999
Tracer	Adults (12)	17 (8–34)	Healthy subjects without a pre-dosing fast. Absorption estimate based on whole body counting.	LeRoy et al. 1966
44 mg, $SrCl_2$	Adults (43M, 20F)	13	Fasted patients with growth hormone deficiency, osteoporosis, hypothyroidism or hypercalcuric urinary tract stones. Absorption estimate based on fraction of dose in plasma at 4 hours.	Sips et al. 1994
219 mg, $SrCl_2$	Adults (6M)	20	Healthy fasted subjects. Absorption estimated from cumulative urinary excretion.	Leeuwenkamp et al. 1990
Tracer in milk	Adults (5)	11	Healthy subjects. Dose administered in milk, daily for 21–32 days. Absorption estimated from whole body retention kinetics.	Rundo and Lilligraven 1966
Tracer	Adults (4F)	42 (25–59)	Two health subjects, two patients with osteoporosis. Absorption estimated from intake minus 20-day fecal excretion, corrected for fecal excretion after an intravenous dose.	Uchiyama et al. 1973
0.8 mg/day diet	Adults (11M)	18 (-17–42)	Patients with various disorders, including osteoporosis. Absorption estimate based on	Warren and Spencer 1976

Table 3-7. Summary of Estimates of Absorption of Ingested Strontium in Humans

Dose and media[a]	Subjects (N)[b]	Absorption (% of dose)[c]	Comment	Reference
			6-day balance; dietary intake minus fecal excretion[e].	
Tracer	Adults (11M)	18 (-17–42)	Patients with various disorders, including osteoporosis. Absorption estimate based on estimated from 6-day balance; dietary intake minus fecal excretion[e].	Warren and Spencer 1976
1,500 mg/day	Adults (5F, 1M)	22 (20–28)	Patients with various illnesses. Absorption estimated from dietary intake minus fecal excretion minus fecal excretion after and I.V. dose (endogenous fecal excretion).	Spencer et al. 1960
Diet	Adults (9)	12 (0–48)	Patients with various illnesses. Absorption estimate based on estimated from 6-day balance; dietary intake minus fecal excretion.[e]	Spencer et al. 1972a
5–100 mg, $SrCl_2$	Children (5) 4–14 years	22	Patients with various illnesses. Dose administered for 24–28 days. Absorption estimated from dose minus 14-day fecal excretion.	Sutton et al. 1971b
100 µg breast milk	Infants 6–8 days (12)	15 (-47–59)	Healthy breast-feeding subjects. Absorption estimate based on estimated from 3-day balance intake minus fecal excretion.[e]	Harrison et al. 1965
600 µg diet	Infants 20 days–1 year (21)	28 (12–43)	Healthy subjects. Absorption estimate based on estimated from seven sequential 28-day balances; dietary intake minus fecal excretion.[e]	Kahn et al. 1969a

[a]Doses are in mass of strontium.
[b]Number of males (M) or females (F) is presented if reported.
[c]Values are reported means ± standard deviation; values in parentheses are reported ranges.
[d]AUC refers to the area under the plasma strontium concentration-time curve.
[e]Calculated from reported individual subject data.

Sutton et al. 1971a). Although age-related changes in strontium absorption cannot be discerned from the studies in humans, age-related changes in absorption of strontium have been observed in rats, suggesting the possibility of increased absorption of strontium during the neonatal period in humans. Adult male rats that received a single oral dose of 1.4 mg Sr as $SrCl_2$ absorbed 19% (±5 standard deviation [SD]) of the dose (Sips et al. 1997); this value is similar to that reported for humans (Sips et al. 1995, 1996).

However, when absorption was estimated at various ages, absorption was found to decrease from 85% of the dose at 15 days of age to 8% of the dose at ages older than 89 days (Forbes and Reina 1972). The differences between the adult estimates in these two studies may reflect the different methodologies; in the Sips et al. (1997) study, absorption was estimated from the area under the plasma strontium concentration-time curve for orally and intravenously administered strontium, whereas in the Forbes and Reina (1972) study, the absorption estimate was based on the measurements of 8-hour body burdens of strontium minus strontium in the gastrointestinal tract.

The fractional absorption of strontium appears to increase in rats during lactation. Rats that received a tracer dose of ^{85}Sr as $SrCl_2$ in drinking water between 14 and 16 days after the start of lactation absorbed twice as much strontium as control rats that were not lactating and received the same oral dose of strontium; 11% of the dose was absorbed in lactating rats compared to 5% in controls (Kostial et al. 1969b). Absorption was estimated in this study as the fraction of the dose in the skeleton, urine, and pups 3 days after the start of exposure.

The exact site of absorption of strontium in the gastrointestinal tract is not known; however, studies in hamsters suggest the possibility of absorption in both the stomach and small intestine. In hamsters that received a gavage tracer dose of $^{85}SrCl_2$, 37% was absorbed, whereas 20% was absorbed when the dose was administered to hamsters that had their pyloric sphincter ligated (Cuddihy and Ozog 1973). Studies in preparations of *in vitro* and *in situ* isolated intestine of the rat provide direct evidence for strontium absorption in the small intestine (see Section 3.6.1).

3.5.1.3 Dermal Exposure

There is little evidence for systemic toxicity following dermal exposure to strontium compounds, which would suggest that they are not readily absorbed across the skin of humans. Ilyin et al. (1975) estimated absorption rates for solutions of strontium chloride across intact or abraded skin of human subjects. Three groups of three male volunteers received topical applications of ^{85}Sr as strontium chloride in

aqueous solution (pH 7.0) without a carrier. In the first group, intact forearm skin (average area 8 cm^2) was exposed for 6 hours. In the second and third groups, the skin of the forearm was abraded with a metal grater just before the solution was applied; exposures were 6.1 cm^2 for 30 minutes and 6.9 cm^2 for 6 hours, respectively. For comparison, a fourth group received an intravenous injection of $^{85}SrCl_2$. After exposure and decontamination of the skin, radioactivity measurements were taken over 40 days of the ^{85}Sr present in the whole body, the patella, the right unexposed forearm, and, during the first 20 days, in daily urine samples. Absorption of strontium was estimated from whole body or partial body ^{85}Sr burdens, or urinary excretion of ^{85}Sr in comparison to the same end points after an intravenous dose of $^{85}SrCl_2$. The absorption of radiostrontium through intact skin over 6 hours was estimated to be 0.26% (range, 0.14–0.37%) of the applied dose, indicating that undamaged skin is a relatively effective barrier to penetration by strontium. Strontium absorption was greater through scratched and abraded skin. An average of 38% (range, 25.5–45.8%) of the applied dose was absorbed after 30 minutes and an average of 57.4% (range of coefficients, 55.7–65.3%) was absorbed after 6 hours. No other studies were located regarding dermal absorption of strontium compounds in humans.

An *in vitro* study evaluated penetration of ^{90}Sr through abdominal skin removed from 5- or 9-day-old Wistar rats and arranged in vertical penetration cells (Bauerová et al. 2001). The radionuclide in a chloride carrier solution (0.01–1.0% strontium chloride w/v) was applied to the epidermal surface; radioactivity of the permeated ^{90}Sr in the receptor chamber solution was measured by liquid scintillation spectrometry. Penetration was inversely related to concentration of the carrier solution. Penetration of the radiostrontium through the hairless skin of 5-day-old rats over 24 hours was 4 times lower than through the hairy skin of 9-day-old rats: at a carrier concentration of 0.1%, penetration was 0.5% for hairless skin of 5-day old rats compared to 2% for 9-day old rats. The authors attributed this difference to the barrier provided by the intact stratum corneum in 5-day skin, indicating that hair follicles in skin of 9-day-old rats increase the permeability of skin to strontium. In experiments in which epidermal layers were stripped (by the 20x repeated application of adhesive tape) or entirely removed from skin of 5-day-old rats, penetration was approximately 25% over 24 hours.

3.5.2 Distribution

3.5.2.1 Inhalation Exposure

Information on the distribution of inhaled strontium in humans is not available; however, it is reasonable to assume that the distribution of strontium absorbed into the systemic circulation after deposition in the respiratory tract would be similar to that absorbed after ingestion (see Section 3.5.2.2).

Studies in animals have shown that strontium that is absorbed after an initial deposition in the respiratory tract ultimately distributes primarily to the skeleton. In dogs that received a 2–22-minute nose-only exposure to aerosols of $^{85}SrCl_2$ (AMAD 1.4–2.7 μm, GSD 2.0), 37% of the body burden was distributed to the skeleton within 12 hours after the exposure and 84% was in the skeleton 4 days after the exposure (Fission Product Inhalation Project 1967a). Four to 6 days after a 30-minute inhalation exposure of rats to aerosols of ^{85}Sr carbonate, phosphate, fluoride, or oxide (particle sizes and doses not specified), >99% of the body burden of ^{85}Sr was in the skeleton (Willard and Snyder 1966). Two days after rats received a 10-minute head-only exposure to tracer levels of ^{85}Sr or a mixture of ^{85}Sr and ^{90}Sr aerosols (AMAD 1.8–2.8), at which time radioactive strontium could no longer be detected in the lung, the concentration in bone was 100–2,000 times that in soft tissues (Fission Product Inhalation Project 1967b). The rank order of soft tissue concentrations (highest to lowest) was muscle > skin > liver > kidney. In rats exposed to airborne fly ash (sieved to have a particle diameter of distribution of 90% less than 20 μm) for 6 hours, strontium was detected in various tissues; 1 day after the exposure, the tissue:plasma strontium concentration ratios were 0.3–0.5 in the liver, kidney, small intestine, and heart (Srivastava et al. 1984b).

Information on the distribution of strontium absorbed after deposition in the respiratory tract can be derived from studies in which strontium compounds were instilled directly into the trachea. Although intratracheal instillation does not precisely replicate inhalation exposure, the distribution of the absorbed strontium is likely to be similar to that which would be absorbed after inhalation. In rats that received an intratracheal dose of ^{89}Sr-enriched fly ash (sieved to have a particle diameter of distribution of 90% less than 20 μm), radioactivity was eliminated from the lung and appeared in plasma and other tissues within days of the exposure; tissue:plasma concentration ratios were >1 (1.5–2) in the liver, kidney, stomach, and small intestine, and <1 (0.7–0.9) in the spleen, heart, and brain (Srivastava et al. 1984a). The relatively high concentrations of strontium in the gastrointestinal tract may reflect the mechanical clearance of strontium from the airways to the esophagus.

Although placental transfer of strontium has been demonstrated in humans and animals exposed to strontium by other routes of exposure (see Section 3.5.2.2), only one study has examined placental transfer after a dose to the respiratory tract. Pregnant rats received an intratracheal dose of ^{89}Sr-enriched fly ash (sieved to have a particle diameter of distribution of 90% less than 20 μm) on days 14–18 of gestation. The concentrations of strontium in whole fetus, liver, lung, heart, and kidney were not significantly different from controls that received an instillation of saline (Srivastava et al. 1990).

3.5.2.2 Oral Exposure

The distribution of absorbed strontium in the human body is similar to that of calcium, with approximately 99% of the total body burden in the skeleton (ICRP 1993). The skeletal burden of stable strontium has been estimated from analyses of bone samples from human autopsies (Herring and Keefer 1971a; O'Connor et al. 1980; Papworth and Vennart 1984; Tanaka et al. 1981). Skeletal burden was estimated in Japanese adult males to be approximately 440 mg compared to 850 g of calcium (Tanaka et al. 1981).

Papworth and Vennart (1984) analyzed published data on ^{90}Sr and calcium concentrations in human bone tissues and diets of people in the United Kingdom during the period from 1955 to 1970 and concluded that approximately 4.75% of the dietary intake of ^{90}Sr was taken up by the adult skeleton. Approximately 7.5% of the cortical bone ^{90}Sr burden was eliminated from bone each year (equivalent to elimination half-times of approximately 9.2 years). The rate of elimination from trabecular bone was approximately 4 times this value. The same analysis yielded estimates of skeletal uptakes of strontium that varied with age, being highest, approximately 10%, in infants and during adolescence, ages in which bone growth rates are high relative to other ages.

Strontium distributes relatively uniformly within the bone volume where it exchanges with calcium in hydroxyapatite (see Section 3.6.1), although small differences in the calcium and strontium distributions within bone have been reported. The Sr:Ca concentration ratio in bone increases with age from approximately 0.3 mg strontium/g Ca at birth to a value of 0.5 in adults (Papworth and Vannart 1984; Tanaka et al. 1981). The Sr:Ca ratio in bone also has been shown to vary with the bone type; ratios in cortical bone were approximately 10–20% higher than in trabecular bone (Tanaka et al. 1981).

Information on the distribution of strontium in soft tissue is extremely limited. In rats that were exposed to 3.4 mg strontium/L (as $SrCl_2$) in drinking water for 3 months, the serum concentration of strontium was

8.7 mg/L and tissue:serum strontium concentration ratios (based on the latter mean serum concentration) were as follows: liver, 0.7; heart, 1.2; muscle, 1.1; adrenal, 1.3; brain, 1.2; and bone, 1,300 (Skoryna 1981b). Strontium:calcium ratios in these tissues were approximately 0.05–0.1. Tissue:plasma strontium concentration ratios in rats 1–5 hours after they received an intraperitoneal injection of strontium revealed ratios <1 in the fat, spleen, liver, ovary, testis, skeletal muscle, and heart; and values of 1.2–1.7 in the lung, small intestine, salivary gland, kidney, and skin (Brues et al. 1969). Tissue:plasma concentration ratios of seminal vesicles in mice increased to values exceeding 2 several days after an intraperitoneal dose of strontium (Brues et al. 1967).

Information on the subcellular location of strontium in soft tissues is also extremely limited. In rats that were exposed to 1.9 mg strontium/L (as $SrCl_2$) in drinking water for 3 months, the strontium concentrations (per mg protein) in the mitochondrial, lysosomal, and microsomal fractions of liver were approximately 5 times that of cytosol (Skoryna 1981b). A major fraction of the strontium in tissues, possibly as much as 50–80% appears to be bound to protein (Kshirsagar 1977).

The partitioning of strontium in blood has not been extensively explored. The concentrations of strontium in the erythrocyte and plasma fractions of human blood obtained from blood banks were 7.2 µg/L in the erythrocyte fraction and 44 µg/L in the plasma fraction, suggesting that most of the strontium in blood resides in the plasma (Olehy et al. 1966). The strontium concentration in serum from 100 human subjects (health status not reported) was 53 µg/L, similar to the value reported for blood bank serum (Skoryna 1981b). Strontium binds to proteins in human serum; however, the specific proteins to which strontium binds have not been characterized. Alda and Escanero (1985) found that 45% of the strontium incubated with human serum at a concentration of 10 mg/L was ultrafilterable. Harrison et al. (1955) reported a value of 60% for the ultrafilterable fraction of plasma at a plasma concentration of 3.5 mg/L in two subjects who received an intravenous dose of 20 or 100 mg strontium chlorides. Note that this concentration is 300–1,000 times that reported for serum concentrations in subjects that were not receiving strontium supplements (Olehy et al. 1966; Skoryna 1981b); at lower concentrations, a larger fraction of the serum strontium may be bound, as binding appears to be saturable (Alda and Escanero 1985; Berg et al. 1973). Values of 40–60% bound to protein have been reported for guinea pig and rabbit plasma or serum, respectively (Lloyd 1968; Twardock et al. 1971).

Strontium in the maternal skeleton can be transferred to the fetus during pregnancy. Studies of residents of the Techa River who were exposed to strontium as result of releases from a plutonium production plant provide evidence for fetal transfer of strontium (Tolstykh et al. 1998, 2001). The fetal:maternal transfer

coefficient—the ratio of ^{90}Sr concentrations in the fetal and maternal skeletons (expressed in becquerels per gram of calcium)—was determined for six subjects who were exposed prior to pregnancy and their seven stillborn infants (Tolstykh et al. 1998). The transfer coefficients varied from 0.012 to 0.24, with the higher values associated with maternal exposures that occurred during adulthood and lower values associated with maternal exposures during childhood or adolescence. The difference was not related to the maternal strontium burden at pregnancy and may reflect a lower availability of strontium deposited in cortical bone during periods of active bone growth.

Studies in animals provide additional evidence for transfer of strontium through the placenta to the fetus. The fetus begins to accumulate strontium as the fetal skeleton develops. In mice, ossification of the fetal skeleton begins on approximately the 14th day of gestation, at which point, the fetal strontium burden begins to increase (Olsen and Jonsen 1979). In pregnant mice that received an injection of strontium at different stages of pregnancy, fetal strontium burden was 4.5% of the maternal dose administered on the 18th day of pregnancy compared to 0.7% of the maternal dose administered on the 14th day of pregnancy (Rönnbäck 1986). Thus, fetal transfer was highest when the maternal dose occurred at the time of greatest skeletal growth. A similar observation has been made in rats; uptake of strontium by the fetus is highest (1–2% of an injected maternal dose) if the maternal dose is given on or after the 16th day of gestation when ossification of the fetal skeleton begins (Hartsook and Hershberger 1973; Wykoff 1971). The distribution of strontium in the fetus at the end of gestation is similar to that of the mother with most of the strontium burden in the skeleton. In mice, the skeletal (long bones):soft tissue concentration ratio was approximately 40 in both the fetuses and dams (Jacobsen et al. 1978).

Strontium enters mammary milk in humans and can be transferred to newborns during breast feeding (Harrison et al. 1965). The concentration of strontium in breast milk of 12 healthy women was estimated to be 74 µg/L (range, 39–93) and the Sr:Ca concentration ratio was 0.24 µg strontium/mg Ca (Harrison et al. 1965). In a study of the transport of trace elements, the concentration of strontium in colostrum samples collected from 29 healthy women during the first 3 days after delivery was found to be comparable to that in serum from venous blood samples taken 20 minutes before delivery (Rossipal et al. 2000). In contrast, the concentration of calcium in colostrum was significantly increased over the level in maternal serum, which was indicative of active transport. The authors concluded that the transfer of strontium was based primarily on a concentration gradient mode of action. Numerous studies in animals provide additional evidence for transfer of strontium from breast milk to newborns during lactation (Hopkins 1967; Jacobsen et al. 1978; Kostial et al. 1969b; Rönnbäck et al. 1968). In lactating rats that received an oral exposure to tracer concentrations ^{85}Sr in drinking water during the 14th through 16th days

of lactation, approximately 5% of the ingested dose was recovered in the nursing pups 24 hours after the end of the 2-day exposure (Kostial et al. 1969b). In a study in which lactating mice received an intraperitoneal injection of radioactive strontium, strontium levels of the nursing pups was approximately 20% of that of the dams (Rönnbäck et al. 1968). These results are consistent with the oral exposure study (Kostial et al. 1969b), if one assumes that approximately 25% of the oral dose was absorbed by the dam. The tissue distribution of strontium in lactating mice and their offspring was found to be similar after an intraperitoneal dose to the dams during lactation; concentrations in bone were approximately 1,000 times higher than liver and kidney (Jacobsen et al. 1978). The strontium concentration in calvaria of the lactating pups, after 5 days of lactation, was approximately 3 times that of the dams, whereas the concentration in long bones of pups and dams were similar (Jacobsen et al. 1978). The difference in the bone concentrations in the dams and pups may reflect the relatively higher rate of bone formation in the pups and associated incorporation of strontium into the new bone.

3.5.2.3 Dermal Exposure

In volunteers who were exposed to dermally applied $^{85}SrCl_2$ in the left forearm, ^{85}Sr was detected by external counting of the patella and right forearm 3 and 6 hours after the exposure was initiated, suggesting that the absorbed strontium had been taken up by bone (Ilyin et al. 1975). Although no other studies were located regarding the distribution of dermally absorbed strontium, it is likely that the distribution would be similar to that absorbed from the oral route, with the most of the body burden in the skeleton (see Section 3.5.2.2).

3.5.3 Metabolism

The metabolism of strontium consists of binding interactions with proteins and, based on its similarity to calcium, probably complex formation with various inorganic anions such as carbonate and phosphate, and carboxylic acids such as citrate and lactate (Alda and Escanero 1985; Inoue et al. 1988; Kshirsagar 1977; Lloyd 1968; Twardock et al. 1971). These types of interactions would be expected for all routes of exposure. These types of interactions would be expected for all routes of exposure including the following:

3.5.3.1 Inhalation Exposure

3.5.3.2 Oral Exposure

3.5.3.3 Dermal Exposure

3.5.4 Elimination and Excretion

3.5.4.1 Inhalation Exposure

Whole body elimination times have been measured in dogs and rats that received inhalation exposures to $SrCl_2$. In dogs that were exposed to aerosols of $^{85}SrCl_2$ (AMAD 1.4–2.7 μm, GSD 2.0), elimination half-times were 0.6 (59%), 9 (12%), and 300 days (29%) (Fission Product Inhalation Project 1967a). The rapid early phase of elimination reflects the mechanical clearance of strontium deposited in the tracheobronchial region of the respiratory tract and transfer to the gastrointestinal tract and feces, whereas the slower elimination component reflects the elimination from the skeleton. A similar pattern of elimination has been observed in rats. In rats that were exposed to tracer levels of ^{85}Sr or a mixture of ^{85}Sr and ^{90}Sr aerosols (AMAD 1.8–2.8), the long-term whole-body elimination half-time, measured 5–230 days after exposure, was 330 days (Fission Product Inhalation Project 1967b).

Strontium that is absorbed after an initial deposition in the respiratory tract is excreted in feces and urine. Evidence for this comes from accidental exposures to radioactive strontium. In one case, a worker accidentally inspired an unknown quantity of $^{90}SrCl_2$ (physical form unknown) and, over the subsequent 800 days, the urinary:fecal excretion ratio was 3:1 (Petkau and Pleskach 1972). The urinary:fecal excretion ratio of 3 is consistent with observations of long-term urinary:fecal excretion ratios observed in people who ingested radioactive strontium or short-term ratios in people who received an intravenous dose of radioactive strontium (see Section 3.5.4.2). In a second case, a worker was exposed to $^{90}SrCO_3$ with deposition within the nasal tract as well as the hands, face, and hair and the urinary:fecal excretion ratio over the first 24 days was 0.71 (Rundo and Williams 1961). The lower ratio in this case probably reflects the fecal contribution of strontium that was mechanically cleared from the respiratory tract over the shorter observation period (24 days compared to 800 days). Similar observations have been made in animals. In dogs that received a 2–22-minute nose-only exposure to aerosols of $^{85}SrCl_2$ (AMAD 1.4–2.7 μm, GSD 2.0), an initially large fecal component of excretion was followed by urinary:fecal excretion ratios of 1.0–1.4 (Fission Product Inhalation Project 1967a). An increase over time in the

urinary:fecal excretion ratios from values <1 to 2–4 has also been observed after intratracheal instillation of $SrCl_2$ in rats (Fission Product Inhalation Project 1967b; Namenyi et al. 1986).

3.5.4.2 Oral Exposure

The long-term (decades) elimination of strontium has been studied in people who were exposed to strontium in the Techa River area of Russia after fission products from a plutonium production process were released in the area. Whole-body elimination half-times were estimated in a study population of 361 males and 356 females to be 28 years in males and 16 years in females (Tolstykh et al. 1997). Most of the difference in the elimination rate estimated for males and females resulted from a pronounced increase in the elimination rate in females after age 50 years. The increase most likely reflects the increase in bone resorption that tends to occur in females after menopause. Müller et al. (1966) estimated a similar value, 25 years, for the long-term elimination half-time of strontium in 56 radium dial painters. In two dial painters, long-term elimination half-times were estimated to be 9 years (Wenger and Soucas 1975). Estimates of the long-term elimination half-times of strontium reflect primarily the storage and release of strontium in bone. Over shorter time periods after exposure, faster elimination rates are observed that reflect soft-tissue elimination as well as elimination from a more rapidly exchangeable pool of strontium in bone. When whole-body elimination of a tracer dose of ^{85}Sr was measured for periods of 42–108 days in nine subjects, the mean elimination half-time was 91 days (±32, SD) (Likhtarev et al. 1975). In three healthy subjects that received a single oral dose of $SrCl_2$, the estimated average whole-body elimination half-times, estimated over 13 days, were 2 (30%) and 59 days (70%) (Uchiyama et al. 1973). Similar short-term rates of elimination have been observed within days to a few weeks after an intravenous injection of $SrCl_2$ (MacDonald et al. 1965; Newton et al. 1990).

Strontium that has been absorbed from the gastrointestinal tract is excreted primarily in urine and feces. In two dial painters, rates of urinary and fecal excretion of radium approximately 10 years after the exposure were approximately 0.03 and 0.01% of the body burden per 24 hours, respectively (Wenger and Soucas 1975). The urine:fecal excretion ratio of 3 that was observed in the radium dial workers is consistent with ratios of 2–6 observed several days to weeks after subjects received an intravenous injection of $SrCl_2$ (Bishop et al. 1960; Blake et al. 1989a, 1989b; Likhtarev et al. 1975; Newton et al. 1990; Samachson 1966; Snyder et al. 1964; Uchiyama et al. 1973). Thus, urine appears to be the major route of excretion of absorbed strontium. The observation of fecal excretion of radioactive strontium weeks to decades after an oral exposure or over shorter time periods after an intravenous exposure suggests the existence of a mechanism for transfer of absorbed strontium into gastrointestinal tract, either

from the bile or directly from the plasma. Evidence for direct secretion of strontium from the plasma into the intestine is provided by studies in animals (see Section 3.5.1). The available information does not address the extent to which biliary excretion may also contribute to fecal excretion of strontium.

As discussed in Section 3.5.2.2, absorbed strontium is eliminated in breast milk during lactation. The concentration of strontium in breast milk of 12 healthy women was estimated to be 74 µg/L (range, 39–93) and the Sr:Ca concentration ratio was 0.24 µg strontium/mg Ca (Harrison et al. 1965).

Strontium has been detected in human saliva and seminal fluid. In healthy subjects who received a single intravenous injection of $SrCl_2$, the saliva:plasma concentration ratio was 0.9 and the semen:plasma ratio was 0.6 (Harrison et al. 1967a).

3.5.4.3 Dermal Exposure

In volunteers who were exposed to dermally applied $^{85}SrCl_2$ in the left forearm, ^{85}Sr was excreted in urine (fecal excretion was not measured in this study) (Ilyin et al. 1975). Although no other studies were located regarding the excretion of dermally absorbed strontium, it is likely that the excretion would be similar to that absorbed from the oral route, with urinary excretion being approximately 2–3 times greater than fecal excretion (see Section 3.5.4.2).

3.5.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target

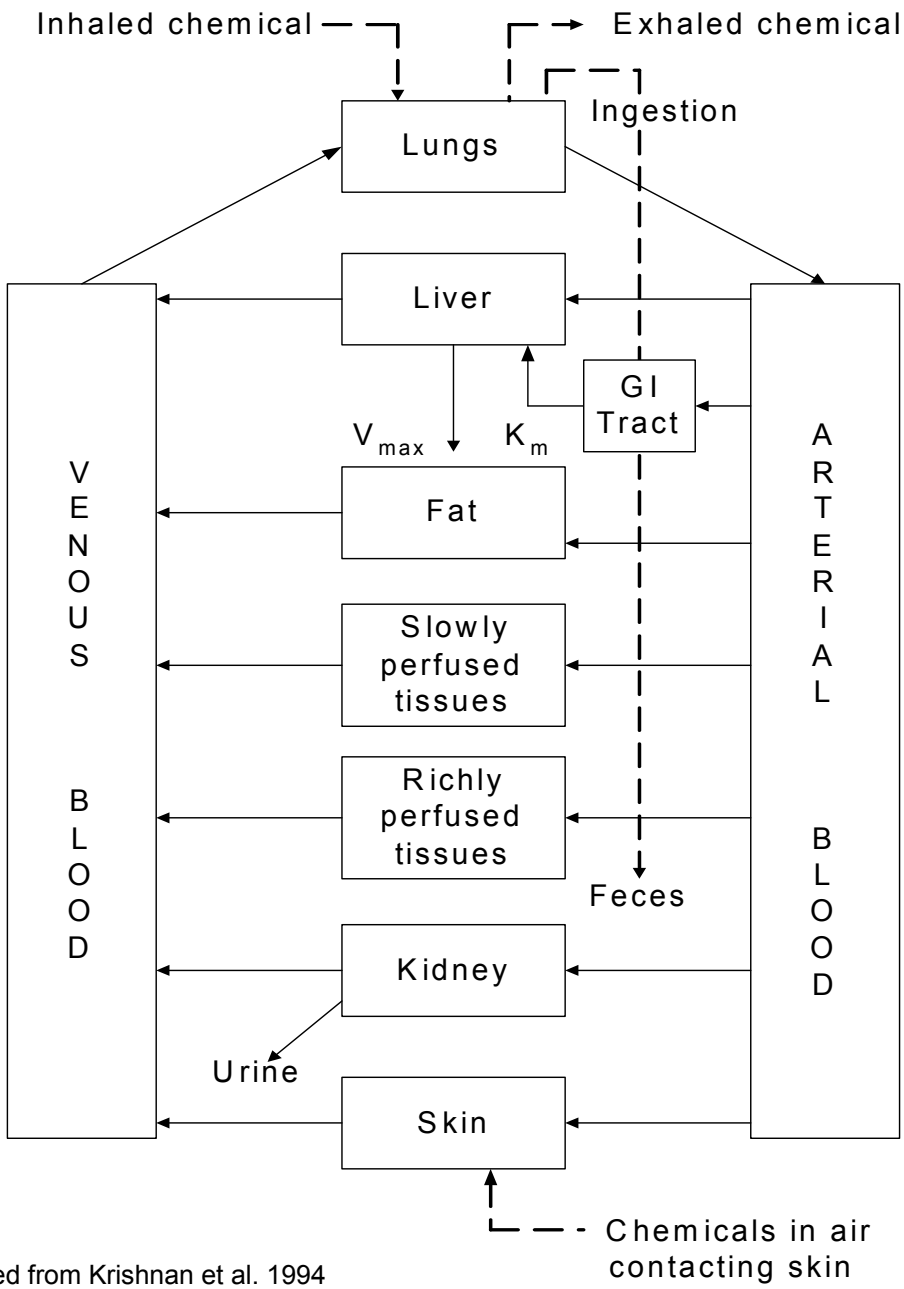
tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). Similar models have been developed for radionuclides. These PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model. Figures 3-5 through 3-8 show models for radionuclides in general or specifically for strontium.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Human Respiratory Tract Model for Radiological Protection (ICRP 1994a).

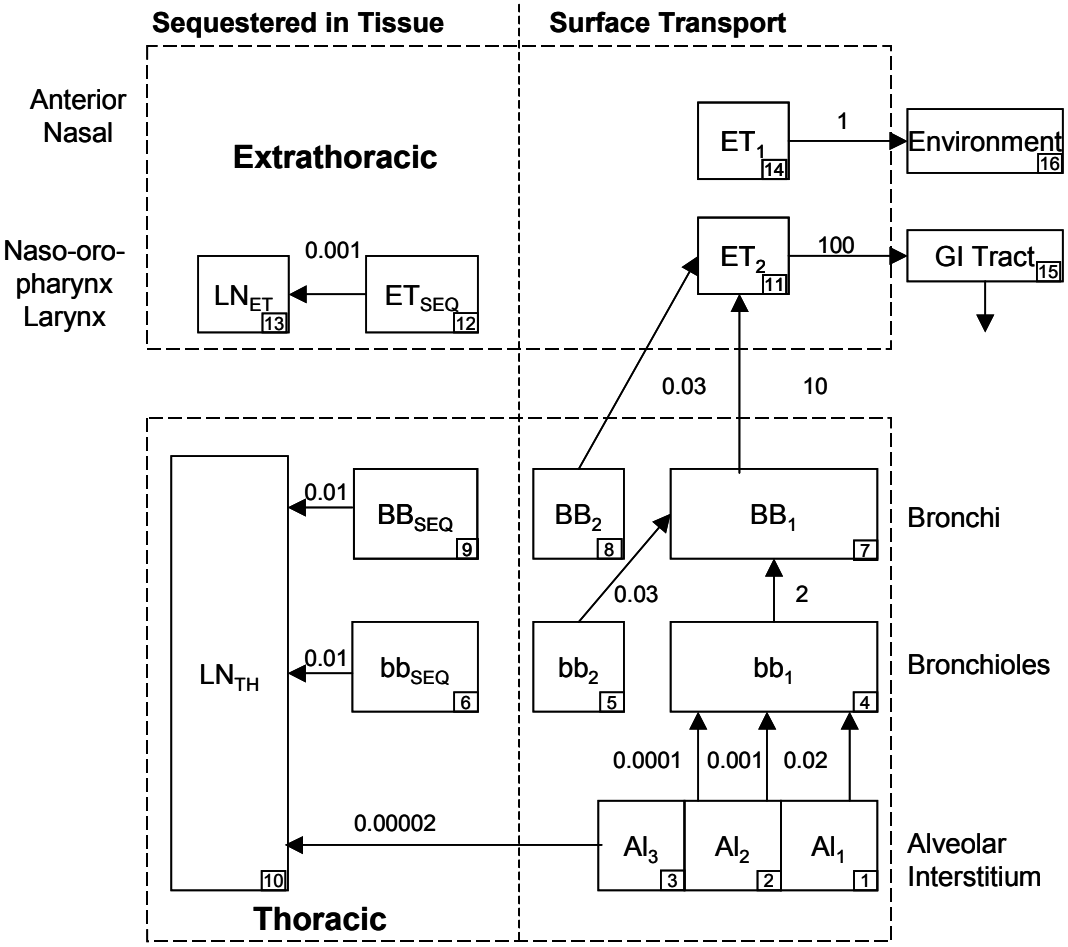
Deposition. The ICRP (1994a) has developed a deposition model for behavior of aerosols and vapors in the respiratory tract. It was developed to estimate the fractions of radioactivity in breathing air that are deposited in each anatomical region of the respiratory tract. ICRP (1994a) provides inhalation dose coefficients that can be used to estimate the committed equivalent and effective doses to organs and tissues throughout the body based on a unit intake of radioactive material. The model applies to three levels of particle solubility and a wide range of particle sizes (approximately 0.0005–100 μm in diameter), and parameter values, which can be adjusted for various segments of the population (e.g., sex, age, level of physical exertion). This model also allows one to evaluate the bounds of uncertainty in deposition estimates. Uncertainties arise from natural biological variability among individuals and the need to interpret some experimental evidence that remains inconclusive. It is applicable to particulate aerosols containing strontium, but was developed for a wide variety of radionuclides and their chemical forms.

The ICRP deposition model estimates the amount of inhaled material that initially enters each compartment (see Figure 3-5). The model was developed with the following 5 compartments: (1) the anterior nasal passages (ET_1); (2) all other extrathoracic airways (ET_2) (posterior nasal passages, the naso- and oropharynx, and the larynx); (3) the bronchi (BB); (4) the bronchioles (bb); and (5) the alveolar interstitium (AI). Particles deposited in each of the regions may be removed from each region and redistributed either upward into the respiratory tree or to the lymphatic system and blood by different particle removal mechanisms.

For extrathoracic deposition of particles, the model uses experimental data, where deposition is related to particle size and airflow parameters, and scales deposition for women and children from adult male data. Similarly, to the extrathoracic region, experimental data served as the basis for lung (bronchi, bronchioles, and alveoli) aerosol transport and deposition. A theoretical model of gas transport and particle deposition was used to interpret data and to predict deposition for compartments and subpopulations other than adult males. Table 3-8 provides reference respiratory values for the general Caucasian population under several levels of activity.

Deposition of inhaled gases and vapors is modeled as a partitioning process which depends on the physiological parameters noted above as well as the solubility and reactivity of compound in the

Figure 3-5. Compartment Model to Represent Particle Deposition and Time-Dependent Particle Transport in the Respiratory Tract*



*Compartment numbers shown in lower right corners are used to define clearance pathways. The clearance rates, half-lives, and fractions by compartment, as well as the compartment abbreviations are presented in Table 3-9.

Source: ICRP 1994a

Table 3-8. Reference Respiratory Values for a General Caucasian Population at Different Levels of Activity

Activity:		Resting (sleeping)			Sitting awake			Light exercise			Heavy exercise		
Maximal workload:		8%			12%			32%			64%		
Breathing parameters:		V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})	V_T (L)	B (m^3h^{-1})	f_R (min^{-1})
Age	Sex												
3 months		0.04	0.09	38	N/A	N/A	N/A	0.07	0.19	48	N/A	N/A	N/A
1 year		0.07	0.15	34	0.1	0.22	36	0.13	0.35	46	N/A	N/A	N/A
5 years		0.17	0.24	23	0.21	0.32	25	0.24	0.57	39	N/A	N/A	N/A
10 years	Male:										0.841	2.22	44
	Both:										0.667	1.84	46
	Female:	0.3	0.31	17	0.33	0.38	19	0.58	1.12	32			
15 years	Male:	0.500	0.42	14	0.533	0.48	15	1.0	1.38	23	1.352	2.92	36
	Female:	0.417	0.35	14	0.417	0.40	16	0.903	1.30	24	1.127	2.57	38
Adult	Male:	0.625	0.45	12	0.750	0.54	12	1.25	1.5	20	1.923	3.0	26
	Female:	0.444	0.32	12	0.464	0.39	14	0.992	1.25	21	1.364	2.7	33

[a]See Annex B (ICRP 1994a) for data from which these reference values were derived.

B = ventilation rate; f_R = respiration frequency; h = hour; min = minute; N/A = not applicable; V_T = tidal volume

respiratory tract (Figure 3-6). The ICRP (1994a) model defines three categories of solubility and reactivity: SR-0, SR-1, and SR-2:

- Type SR-0 compounds include insoluble and nonreactive gases (e.g., inert gases such as H_2, He). These compounds do not significantly interact with the respiratory tract tissues and essentially all of the compound that is inhaled is exhaled. Radiation doses from inhalation of SR-0 compounds are assumed to result from the irradiation of the respiratory tract from the air spaces.

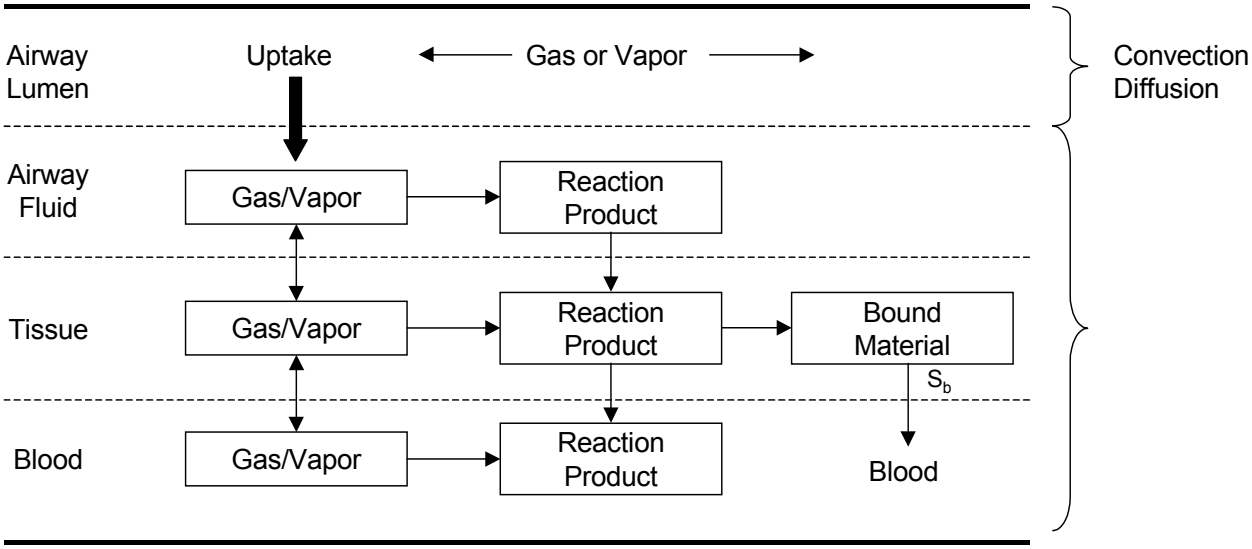
- Type SR-1 compounds include soluble or reactive gases and vapors that are expected to be taken up by the respiratory tract tissues and may deposit in any or all of the regions of the respiratory tract, depending on the dynamics of the airways and properties of the surface mucous and airway tissues, as well as the solubility and reactivity of the compound.

- Type SR-2 compounds include soluble and reactive gases and vapors that are completely retained in the extrathoracic regions of the respiratory tract. SR-2 compounds include sulfur dioxide (SO2) and hydrogen fluoride (HF).

Mechanical Clearance from the Respiratory Tract. This portion of the model identifies the principal clearance pathways within the respiratory tract. The model was developed to predict the retention of various radioactive materials. Figure 3-7 presents the compartmental model and is linked to the deposition model (Figure 3-5) and to reference values presented in Table 3-9. Table 3-9 provides clearance rates and deposition fractions for each compartment for insoluble particles. The table provides rates of insoluble particle transport for each of the compartments, expressed as a fraction per day and also half-time. ICRP (1994a) also developed modifying factors for some of the parameters, such as age, smoking, and disease status. Parameters of the clearance model are based on human evidence for the most part, although particle retention in airway walls is based on experimental data from animal experiments.

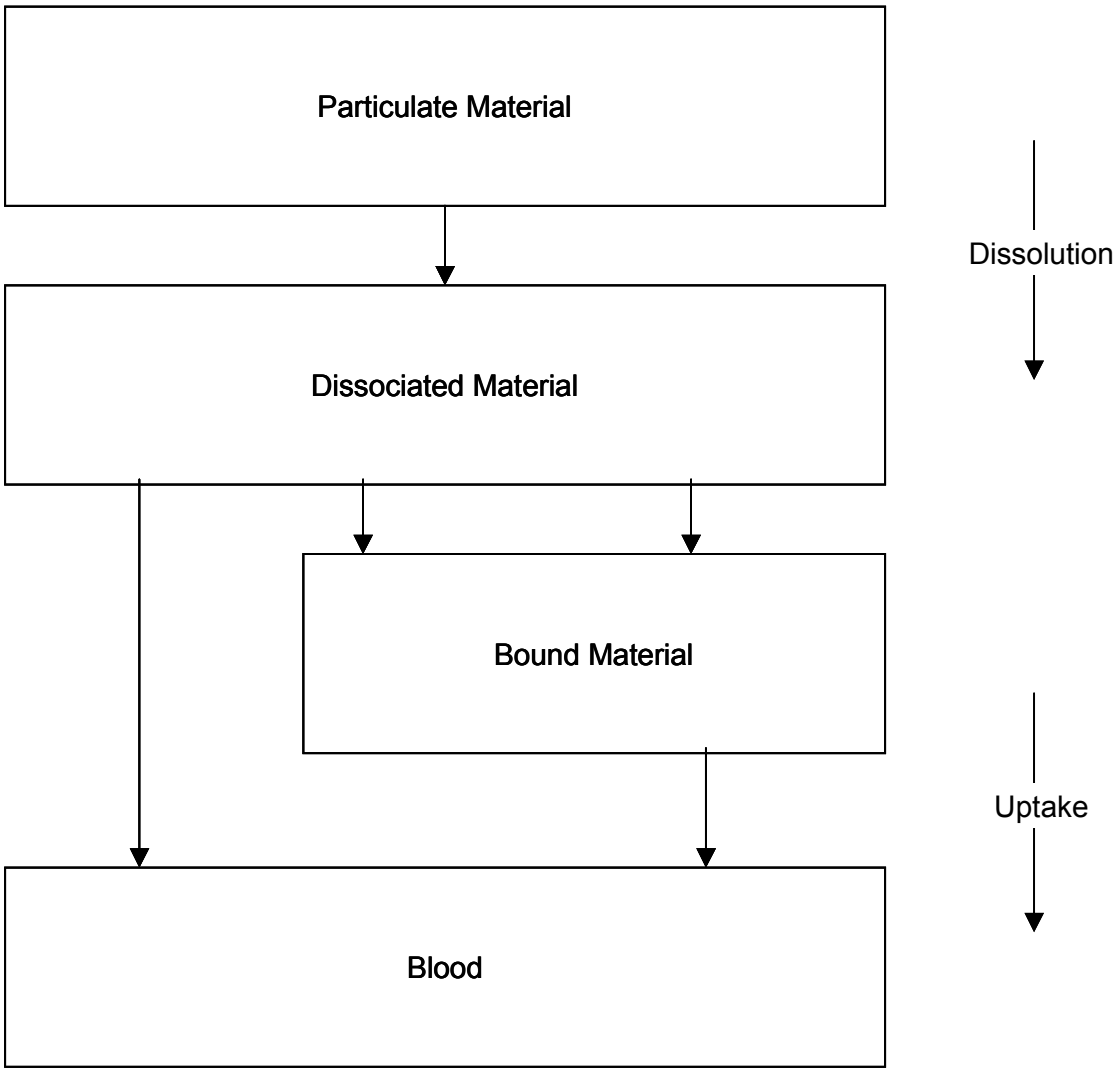
The clearance of particles from the respiratory tract is a dynamic process. The rate of clearance generally changes with time from each region and by each route. Following deposition of large numbers of particles (acute exposure), transport rates change as particles are cleared from the various regions. Physical and chemical properties of deposited material determine the rate of dissolution and as particles dissolve, absorption rates tend to change over time. By creating a model with compartments of different clearance rates within each region (e.g., BB_1, BB_2, BB_{seq}), the ICRP model overcomes problems associated with time-dependent functions. Each compartment clears to other compartments by constant rates for each pathway.

Figure 3-6. Reaction of Gases or Vapors at Various Levels of the Gas-Blood Interface



From ICRP 1994a

Figure 3-7. The Human Respiratory Tract Model: Absorption into Blood



Source: ICRP 1994a

Table 3-9. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part A

	Clearance rates for insoluble particles			
Pathway	From	To	Rate (d^{-1})	Half-time[a]
$m_{1,4}$	AI_1	bb_1	0.02	35 days
$m_{2,4}$	AI_2	bb_1	0.001	700 days
$m_{3,4}$	AI_3	bb_1	0.0001	7,000 days
$m_{3,10}$	AI_3	LN_{TH}	0.00002	No data
$m_{4,7}$	bb_1	BB_1	2	8 hours
$m_{5,7}$	bb_2	BB_1	0.03	23 days
$m_{6,10}$	bb_{seq}	LN_{TH}	0.01	70 days
$m_{7,11}$	BB_1	ET_2	10	100 minutes
$m_{8,11}$	BB_2	ET_2	0.03	23 days
$m_{9,10}$	BB_{seq}	LN_{TH}	0.01	70 days
$m_{11,15}$	ET_2	GI tract	100	10 minutes
$m_{12,13}$	ET_{seq}	LN_{ET}	0.001	700 days
$m_{14,16}$	ET_1	Environment	1	17 hours

Table 3-9. Reference Values of Parameters for the Compartment Model to Represent Time-dependent Particle Transport from the Human Respiratory Tract

Part B

Partition of deposit in each region between compartments[b]		
Region or deposition site	Compartment	Fraction of deposit in region assigned to compartment[c]
ET_2	ET_2	0.9995
	ET_{seq}	0.0005
BB	BB_1	0.993-f_s
	BB_2	f_s
	BB_{seq}	0.007
bb	bb_1	0.993-f_s
	bb_2	f_s
	bb_{seq}	0.007
AI	AI_1	0.3
	AI_2	0.6
	AI_3	0.1

[a]The half-times are approximate since the reference values are specified for the particle transport rates and are rounded in units of d^{-1}. A half-time is not given for the transport rate from AI_3 to LN_{TH}, since this rate was chosen to direct the required amount of material to the lymph nodes. The clearance half-time of compartment AI_3 is determined by the sum of the clearance rates from it.
[b]See paragraph 181, Chapter 5 (ICRP 1994a) for default values used for relating f_s to d_{ae}.
[c]It is assumed that the slow-cleared fraction f_s is size-dependent. For modeling purposes f_s is taken to be:

$$f_s = 0.5 \ for \ d_{ae} \le 2.5\sqrt{\rho/\chi}\ \mu m \ \ and$$
$$f_s = 0.5e^{0.63(d_{ae}\sqrt{\rho/\chi}-2.5)} \ \ for \ d_{ae} > 2.5\sqrt{\rho/\chi}\ \mu m$$

AI = alveolar-interstitial region; BB = bronchial region; bb = bronchiolar region; BB_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchial region; bb_{seq} = compartment representing prolonged retention in airway walls of small fraction of particles deposited in the bronchiolar region; d = day(s); ET = extrathoracic region; ET_{seq} = compartment representing prolonged retention in airway tissue of small fraction of particles deposited in the nasal passages; GI = gastrointestinal; LN_{ET} = lymphatics and lymph nodes that drain the extrathoracic region; LN_{TH} = lymphatics and lymph nodes that drain the thoracic region

Source: ICRP 1994a

Particle transport from all regions is toward both the lymph nodes and the pharynx, and a majority of deposited particles end up being swallowed. In the front part of the nasal passages (ET_1), nose blowing, sneezing, and wiping remove most of the deposited particles. Particles remain here for about a day. For particles with AMADs a few micrometers or greater, the ET_1 compartment is probably the largest deposition site. A majority of particles deposited at the back of the nasal passages and in the larynx (ET_2) are removed quickly by the fluids that cover the airways. In this region, particle clearance is completed within 15 minutes.

Ciliary action removes deposited particles from both the bronchi and bronchioles. Though it is generally thought that mucocilliary action rapidly transports most particles deposited here toward the pharynx, a fraction of these particles are cleared more slowly. Evidence for this is found in human studies. For humans, retention of particles deposited in the lungs (BB and bb) is apparently biphasic. The "slow" action of the cilia may remove as many as half of the bronchi- and bronchiole-deposited particles. In human bronchi and bronchiole regions, mucus moves more slowly the closer it is to the alveoli. For the faster compartment, it has been estimated that it takes about 2 days for particles to travel from the bronchioles to the bronchi and 10 days from the bronchi to the pharynx. The second (slower) compartment is assumed to have approximately equal fractions deposited between BB_2 and bb_2, and both with clearance half-times estimated at 20 days. Particle size is a primary determinant of the fraction deposited in this slow thoracic compartment. A small fraction of particles deposited in the BB and bb regions is retained in the airway wall for even longer periods (BB_{seq} and bb_{seq}).

If particles reach and become deposited in the alveoli, they tend to stay imbedded in the fluid on the alveolar surface or move into the lymph nodes. The one mechanism by which particles are physically resuspended and removed from the AI region is coughing. For modeling purposes, the AI region is divided into three subcompartments to represent different clearance rates, all of which are slow.

Particle clearance from the alveolar-interstitial region has been measured in human subjects. The ICRP model uses two half-times to represent clearance: about 30% of the particles have a 30-day half-time, and the remaining 70% are given a half-time of several hundred days. Over time, AI particle transport falls, and some compounds have been found in lungs 10–50 years after exposure.

Absorption into Blood. The ICRP model assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages (ET_1), where no absorption occurs. Absorption is essentially a 2-stage process, as shown in Figure 3-7. First, there is a dissociation

(dissolution) of particles; then, the dissolved molecules or ions diffuse across capillary walls and are taken up by the blood. Immediately following dissolution, rapid absorption is observed. For some elements, rapid absorption does not occur because of binding to respiratory-tract components. In the absence of specific data for specific compounds, the model uses the following default absorption rate values for those specific compounds that are classified as Types F (fast), M (medium), S (slow), and V (instantaneous):

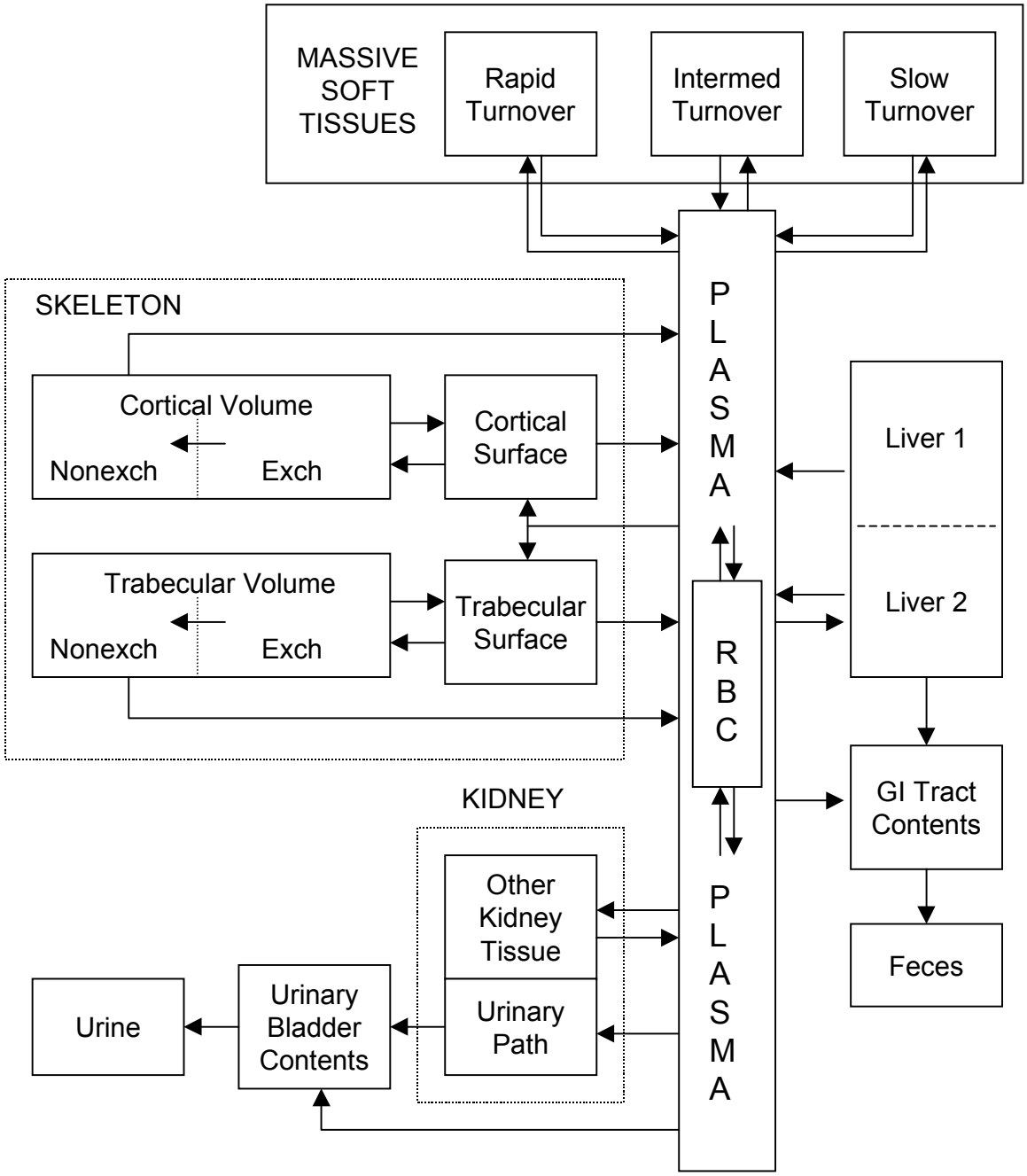
- For Type F, there is rapid 100% absorption within 10 minutes of the material deposited in the BB, bb, and AI regions, and 50% of material deposited in ET_2. Thus, for nose breathing, there is rapid absorption of approximately 25% of the deposit in ET and 50% for mouth breathing.
- For Type M, about 70% of the deposit in AI reaches the blood eventually. There is rapid absorption of about 10% of the deposit in BB and bb, and 5% of material deposited in ET_2. Thus, there is rapid absorption of approximately 2.5% of the deposit in ET for nose breathing, and 5% for mouth breathing.
- For Type S, 0.1% is absorbed within 10 minutes and 99.9% is absorbed within 7,000 days, so there is little absorption from ET, BB, or bb, and about 10% of the deposit in AI reaches the blood eventually.
- For Type V, complete absorption (100%) is considered to occur instantaneously.

ICRP (1995) considers the experimental data on strontium carbonate, and chloride, and sulfate to support classification of these compounds as Type F. Data on strontium particulates released from irradiated fuel support their classification as either Type F or M. Data on strontium in fused aluminosilicate particles support a classification as Type S. ICRP (1995) recommends assigning all strontium aerosols to Type M in the absence of specific information supporting an alternative classification.

ICRP (1993) Strontium Biokinetics Model

Description of the model. ICRP (1993) developed a compartmental model of the kinetics of alkaline earth elements, including strontium, in humans that is applicable to infants, children, adolescents, and adults. The model is based on a nearly identical model developed by Leggett (1992). The fraction of ingested strontium that is absorbed (uptake to blood) is assumed to vary with age and have values of 0.6 in infants up to 12 months of age, 0.4 from 12 months of age through 15 years, and 0.3 from age 15 years through adulthood. Absorbed strontium that enters the blood plasma is assumed to distribute to the skeleton, liver, and other tissues (Figure 3-8). Excretion pathways included in the model are plasma to urine, plasma to feces, and liver to feces. Transfer rate coefficients between compartments are age-specific and, depending on the specific coefficient, values can change at ages 3 months, 1 year, 5 years, 10 years, 15 years, and adult (>15 years). The model assumes that 99% of the strontium that enters the

Figure 3-8. ICRP (1993) Model of Strontium Biokinetics



body and is not excreted is ultimately transferred to the skeleton and 1% is in soft tissues. Skeletal deposition is assumed to distribute initially to the bone surface of either cortical or trabecular bone, from which it can exchange relatively rapidly with calcium in plasma or more slowly with calcium in the bone volume. Two pools are assumed to exist within the bone volume, an exchangeable pool that communicates with surface bone, and a nonexchangeable pool from which strontium can be returned to plasma as a result of bone resorption. Approximately 55% of the transfer from plasma to bone in adults is to the trabecular bone surface and 45% to the cortical bone surface.

Validation of the model. The extent to which the ICRP model has been validated is not described in ICRP (1993).

Risk assessment. The model has been used to establish radiation dose equivalents (Sv/Bq) of ingested ^{89}Sr and ^{90}Sr for ages 3 months to 70 years (ICRP 1993). The model has also been applied by the ICRP to calculate limits on inhalation for ^{89}Sr and ^{90}Sr (ICRP 1995) and limits on inhalation or ingestion for ^{80}Sr, ^{81}Sr, ^{82}Sr, ^{83}Sr, ^{85}Sr, ^{85m}Sr, ^{87m}Sr, ^{91}Sr, and ^{92}Sr (ICRP 1994b). It was used in the U.S. Federal Guidance Report No. 13 (EPA 2000e) to calculate inhalation risk coefficients and ingestion risk coefficients (separately for food and water) for the following radionuclides: ^{80}Sr, ^{81}Sr, ^{82}Sr, ^{83}Sr, ^{85}Sr, ^{85m}Sr, ^{87m}Sr, ^{89}Sr, ^{90}Sr, ^{91}Sr, and ^{92}Sr.

Target tissues. The model is designed to calculate ^{89}Sr and ^{90}Sr intake limits, based on radiation dose to all major organs, including the bone surfaces, bone marrow, and liver, to which the highest doses would be expected.

Species extrapolation. The model is designed for applications to human dosimetry and cannot be applied to other species without modification.

Interroute extrapolation. The model is intended for application to strontium reaching blood by absorption from lungs, gastrointestinal tract, or wound, or by injection.

3.6 MECHANISMS OF ACTION

3.6.1 Pharmacokinetic Mechanisms

Absorption. Airborne particulate aerosols of strontium can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulates in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs mouth breathing), airway geometry, and airstream velocity within the respiratory tract (Gehr 1994; James et al. 1994; Roy et al. 1994). In general, large particles (>2.5 μm) deposit in the nasopharyngeal tract where high airstream velocities and airway geometry facilitate inertial impaction (Chan and Lippman 1980; James et al. 1994). In the tracheobronchial and alveolar regions, where airstream velocities are lower, processes such as sedimentation and interception become important for deposition of smaller particles (<2.4 μm). Breathing patterns, airflow velocity, and airway geometry change with age, giving rise to age-related differences in particle deposition (James 1978; James et al. 1994; Phalen et al. 1985). Deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986). Absorption of insoluble strontium is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles (>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Particles deposited in the alveolar region can be absorbed after extracellular dissolution or ingestion by phagocytic cells. Strontium-bearing pulmonary alveolar macrophages (PAMs) can migrate either to the airways where mucocilliary transport to the esophagus can occur or to tracheobronchial lymph nodes. The relative contributions of these two pathways to strontium absorption have not been quantified.

The exact site of absorption of strontium in the gastrointestinal tract is not known; however, studies in hamsters suggest the possibility of absorption in both the stomach and small intestine. In hamsters that received a gavage tracer dose of $^{85}SrCl_2$, 37% was absorbed, whereas 20% was absorbed when the dose was administered to hamsters that had their pyloric sphincter ligated (Cuddihy and Ozog 1973). In isolated, everted segments of small intestine of the rat, transfer from the mucosal (lumen) to the serosal (blood) side of the duodenum, jejunum, and ileum was observed. The serosal:mucosal strontium concentrations were approximately 0.2–0.4, whereas the ratio for calcium in preparations of duodenum was 1.98 (Stantic and Gruden 1974). Ratios >1 would be indicative of an active transport process; therefore, this study did not detect an active component of strontium transfer across the small intestine.

Measurements of the rate of uptake of strontium into slices of rat small intestine when incubated with increasing concentrations of strontium suggested the existence of a saturable uptake mechanism in the intestinal epithelium (Papworth and Patrick 1970). The fractional absorption of a gavage dose of strontium appears to be a relatively constant ratio to that of calcium. In rats, the strontium:calcium absorption ratio was 0.75 over a fairly wide range of absorbed fractions of calcium (Marcus and Wasserman 1965). This suggests that strontium and calcium may be absorbed by similar mechanisms. Strontium has been shown to be a substrate for a Ca^{2+}-ATPase on the basolateral membrane of the renal proximal tubule in the rat, which is thought to play an important role in the tubule reabsorption of calcium (Sugihira et al. 1992).

Active vitamin D (calcitriol or $1,25(OH)_2D_3$) has an indirect, delayed effect on the gastrointestinal absorption of strontium or calcium by inducing the synthesis of calcium-binding proteins in both humans and animals (Bianchi et al. 1999). A calcitriol-inducible Ca^{2+}-ATPase has been shown to be important in the absorption of calcium in the rat intestine, and may provide a common mechanism for absorption of calcium and strontium (Bronner et al. 1986). Other possible common mechanisms may involve binding of calcium and strontium to an intracellular calcium-binding protein, calbindin-D, which is a $1,25(OH)_2D_3$-inducible calcium binding protein that is thought to play an important role in calcium absorption (Gross and Kumar 1990). In a group of 18 66-year-old women who received calcitriol at a daily dose of 0.5 μg of calcitriol for two years, the intestinal absorption of strontium was 13.7% compared to 10.4% for the untreated controls (Sairanen et al. 2000); the basal absorption percentages before treatment were 8.7 and 9.2%, respectively. Age-related decreases in the gastrointestinal absorption of strontium in men (ages 20–79) were found to be positively correlated with serum levels of insulin-like growth factor I (IGF-I) (Fatayerji et al. 2000). These authors proposed that IGF-I increases strontium absorption by maintaining the structural integrity of the intestine and the sensitivity of the intestine to $1,25(OH)_2D$ and increasing the synthesis of calcium-binding protein in that tissue. IGF-I also acts by stimulating the synthesis of $1,25(OH)_2D$ in the kidney (Audi et al. 1999; Fatayerji et al. 2000).

Distribution. The close similarity in the distribution of strontium and calcium derives from the ability of strontium to interact with ligands that normally bind calcium (Skoryna 1981b). These include hydroxyapatite, the main component of mineralized bone (Harrison et al. 1959; Schoenberg 1963) and a variety of calcium binding and transport proteins that are important in the physiological disposition of calcium in cells, including Ca^{2+}-ATPases (Berman and King 1990; Mermier and Hasselbach 1976; Pfleger and Wolf 1975; Sugihira et al. 1992; Yu and Inesi 1995), Na^{+}-Ca^{+}-antiport (McCormack and

Osbaldeston 1990; Niggli 1989; Richard et al. 1989), and Ca^{2+} channels (Fukushi et al. 1995a, 1995b; Gregoire et al. 1993).

Metabolism. As noted in Section 3.5.3, the metabolism of strontium consists of binding interactions with proteins and probably complex formation with various inorganic anions such as carbonate and phosphate, and carboxylic acids such as citrate and lactate.

Excretion. The renal clearance of strontium has been measured in human subjects who received an intravenous injection of a dose of $SrCl_2$ and is approximately 4–10 L/day and 2–3 times greater than renal calcium clearance (Blake et al. 1986, 1989a, 1989b; Harrison et al. 1955, 1966a; Newton et al. 1990; Samachson 1966). Based on these estimates, the renal clearance of strontium is substantially less than the product of the glomerular filtration rate in humans (approximately 180–200 L/day) and the estimated rate of filtration of strontium, assuming that approximately 50% of the strontium in plasma is ultrafilterable (Harrison et al. 1955). Thus, strontium appears to undergo net tubular reabsorption in the human kidney. The mechanism by which strontium is reabsorbed in the renal tubule has not been determined, although it is likely that it may share common transport mechanisms with calcium, possibly including the Na^{+}-Ca^{2+}-antiport, Ca^{2+}-ATPase and membrane Ca^{2+} channels, all of which are thought to play a role in the reabsorption of calcium (Friedman and Gesek 1995). Direct evidence for this comes from *in vitro* studies of basolateral membranes isolated form the rat renal cortex (primarily proximal tubule). In this preparation, strontium has been shown to be a substrate for a Ca^{2+}-ATPase, which transports calcium from the proximal tubular cells into the plasma (Sugihira et al. 1992).

The observation of fecal excretion of radioactive strontium for weeks to decades after an oral exposure or over shorter time periods after an intravenous exposure suggests the existence of a mechanism for transfer of absorbed strontium into gastrointestinal tract, either from the bile or directly from the plasma. Evidence for direct secretion of strontium from the plasma into the intestine is provided by studies conducted with the *in situ* lumen-perfused rat intestine. When the lumen of either the small or large intestine was perfused (below the entrance of the bile duct) *in situ*, and radioactive strontium was injected intravenously, radioactive strontium was detected in the lumen, indicating that strontium was secreted from blood into the intestine (Palmer and Thompson 1961). The amount of strontium secreted into the small intestine was approximately 4–8 times that in the large intestine; however, the strontium:calcium secretion ratio was approximately 1 in the small intestine and 1.3 in the large intestine. The mechanism by which strontium is secreted into the intestine has not been determined. Transfer of strontium from the serosal (blood) side of the intestinal epithelium to the mucosal (lumen) side of the epithelium has been

demonstrated in *in vitro* preparations of isolated rat colon mucosa. Serosal-to-mucosal transfer was observed to be completely dependent on the transepithelial electrochemical potential for strontium, completely insensitive to calcium concentration of the serosal bathing medium, and unaffected by prior treatment of the rats with 1,2,-dihydroxyvitamin D_3, which stimulated calcium transport in the same preparation (Karbach and Rummel 1987). Based on these observations, transfer of strontium into the lumen of the colon in this preparation appeared to be explainable as a passive process.

3.6.2 Mechanisms of Toxicity

The fact that strontium is chemically similar to calcium allows it to exchange for calcium in bone and other cellular compartments that are enriched in calcium. Many enzymes that are calcium-dependent will function when strontium is substituted, but changes in kinetic parameters may occur. As discussed in Section 3.6.1, strontium can interact with secondary cell messenger systems and transporter systems that normally use calcium. Furthermore, as described in Section 3.2.4 (Neurological Effects), synaptic transmission may be variably affected by strontium. Consequently, at high concentrations, differences in the chemical characteristics between strontium and calcium may be the basis for neurotoxic and neuromuscular perturbations associated with strontium intoxication.

Effect of Metabolism on Toxicity. Variations in the rate of absorption of soluble strontium compounds will affect the severity of their effects following oral exposure. One report identified polymorphisms in three alleles for the vitamin D receptor that imparted a 40% difference in efficiency in intestinal strontium absorption in humans (Gennari et al. 1997). The significance of this finding is unresolved, since other studies have found no link between vitamin D receptor genotypes and enteral absorption rates for calcium or strontium (Vezzoli et al. 2002; Wolf et al. 2000). Furthermore, no association was found between vitamin D receptor polymorphisms and bone mineral density when other parameters are taken into consideration (Poggi et al. 1999). However, daily administration of 0.5 μg of activated vitamin D to 66-year-old women over 2 years increased both the rate of strontium absorption and the bone mineral density at the femoral neck and the lumbar spine (Sairanen et al. 2000). The rate of strontium incorporation into bone may be influenced by other factors thought to affect bone mineralization, such as parathyroid hormone receptor, estrogen receptor 1, and others (Audi et al. 1999; Duncan et al. 1999). However, the effects of these factors on strontium utilization have not been established definitively. Genetic variants of the parathyroid hormone receptor 1 result in either increased or decreased bone mineralization (Duncan et al. 1999). There is a potential physiological link between the estrogen receptor and vitamin D in osteoblasts, although the relationship to bone mineralization has not been established

(Audi et al. 1999); vitamin D regulates the expression of P450 aromatase, an enzyme expressed in osteoblasts that modulates the availability of estrogen to its receptor. The cytokine interleukin-6 is associated with osteoclast differentiation, and therefore, could potentially be involved with the removal of strontium from bone (Audi et al. 1999; Duncan et al. 1999). Persons with chronic kidney failure may be more susceptible to effects of excess strontium because of a reduced ability to excrete strontium (Apostolidis et al. 1998; see Section 3.12); in this study, plasma levels of strontium were 60% higher in afflicted patients compared to controls. A study in rats demonstrated that protein deficiency, especially in combination with ethanol consumption, may increase strontium incorporation into bone while reducing fecal and urinary excretion of strontium (Gonzales-Reimers et al. 1999; see Section 3.12).

Differences in bone physiology suggest that adult rats may have a higher susceptibility to stable or radioactive strontium effects than adult humans. Unlike most mammals (including humans), the epiphyseal growth plate of the long bones of rats never entirely transforms into bone after sexual maturity, so that bone growth continues throughout life (although reduced after the age of 12 months) (Leininger and Riley 1990). Thus, incorporation of strontium into the skeleton is likely to be relatively higher in adult rats compared to other mammals.

Stable Strontium. The toxicity of excess stable strontium is related to its interference in biological processes that normally involve calcium, most notably, skeletal development.

Calcium Absorption. In animals, excess strontium indirectly suppresses the activation of vitamin D_3 in the kidney, which severely reduces the expression of calbindin D mRNA and the translation of calbindin D protein in the duodenum (Armbrecht et al. 1979, 1998; Omdahl and DeLuca 1972). As a result, duodenal absorption of calcium is reduced. The reported inverse correlation between the amount of strontium that is absorbed and the levels of parathyroid hormone (Vezzoli et al. 1998) suggest that changes in parathyroid hormone levels mediate this effect. While there are no data on strontium-binding to the calcium receptor of the parathyroid gland, it is likely that strontium binds in place of calcium, mimicking calcium and thereby suppressing parathyroid hormone levels. A reduction in parathyroid hormone levels will decrease the level of 1-hydroxylase available to activate vitamin D_3.

Bone Toxicity. In addition to its effect on calcium absorption, excess absorbed strontium adversely affects bone development in several ways, leading to the development of rickets in young laboratory animals and possibly in children under special circumstances (Özgür et al. 1996). Strontium binds directly to hydroxyapatite crystals, which may interfere with the normal crystalline structure of bone

(Storey 1961). In addition, excess strontium may prevent the normal maturation of chondrocytes in the epiphyseal plates of long bones (Matsumoto 1976). Excess strontium apparently interferes with the mineralization of complexed acidic phospholipids that is thought to help initiate the formation of hydroxyapatite crystals in developing bone (Neufeld and Boskey 1994). As a result, affected bone contains an excess of complexed acidic phospholipid and a significantly lower ash weight. Insufficient mineralization reduces the strength of bones, so that the inability to resist compression from increasing body weight results in bone distortion (bowing).

Anaphylactic Response After Inhalation Exposure. There was one case of anaphylaxis reported in a paramedic who inhaled strontium-containing smoke in an enclosed space (Federman and Sachter 1997; see Section 3.2.1.2). Although other irritants in the smoke may have contributed to the incident, there is supporting evidence that large concentrations of stable strontium can stimulate the release of histamine from mast cells (Alm and Bloom 1981a, 1981b; Atkinson et al. 1979; Foreman 1977; Foreman and Mongar 1972a, 1972b; Foreman et al. 1977). Stable strontium stimulates degranulation in several cell types (see Section 3.2.5 Hematological Effects) and it has been suggested that it acts by mimicking the receptor-linked rise in calcium that is the usual trigger for such events (Best et al. 1981). It is conceivable that the conditions of the paramedic's exposure were such to result in locally high concentrations of strontium in the respiratory tract, thereby eliciting histamine release and contraction of smooth muscle.

Radioactive Strontium. The adverse health effects of radioactive strontium are related to its sequestration in bone, the high energy of its beta emissions, and, in the case of ^{90}Sr, its long half-life and the radiation from the decay product, ^{90}Y, produced in the body after intake of ^{90}Sr. An extensive discussion of ionizing radiation and its health effects is found in the Appendix D of this document and in the Toxicological Profile for Ionizing Radiation (Agency for Toxic Substances and Disease Registry 1999). There is some evidence that body size or skeletal density may affect the outcome of exposures to radioactive strontium. It was suggested that two cows that survived large oral doses of ^{90}Sr owed their survival to their breed characteristics (Cragle et al. 1969). The massive skeletons of Holsteins have wide bone marrow cavities so that tissue in the center of the bone marrow is not within range of the 1 cm beta emissions from radiostrontium (and radioyttrium) bound to bone. Conversely, mice and rats are more vulnerable than large animals to radioactive strontium because all bone marrow tissues are within striking range. This renders rats and mice less useful than larger mammals as models for human exposure to radioactive strontium. In addition, adult rats are less satisfactory models than adults of other species because of the persistence of the epiphyseal cartilaginous plate, which will result in the incorporation of larger amounts of radioactive strontium into bone.

Bone Toxicity. Beta emissions from radiostrontium bound to bone resulted in various bone lesions (trabecular osteoporosis, sclerosis, osteolytic lesions), particularly in animals that were exposed chronically (Book et al. 1982; Clarke et al. 1972; Momeni et al. 1976). In young rats and rabbits exposed orally to ^{90}Sr, necrotic effects on the vasculature of developing bone secondarily disrupted the process of osteogenesis (Casarett et al. 1962; Downie et al. 1959). Disruption in the metaphyseal microvasculature disorganized the transformation of cartilage into bone, so that chondrocytes inappropriately resumed active proliferation.

Pancytopenia. The severe reduction in hematopoetic tissue results from irradiation of the bone marrow by radiostrontium incorporated into bone. At high exposure levels, thrombocytopenia may lead to platelet loss severe enough to cause hemorrhaging and the resulting anemia will be exacerbated by destruction of erythropoietic tissue. Impaired immune function results from the genetic damage to lymphocytes.

Carcinogenicity. Radioactive strontium is a genotoxic carcinogen. Following exposure *in vivo*, cytogenetic analysis has revealed aneuploidy, chromosomal breaks, gaps, rings, and exchanges (see Table 3-5), which are manifestations of unrepairable changes in DNA. It is generally understood that radiation-induced damage to genes that regulate cell growth is a major factor in the development of cancer in affected cells, and the observation of chromosomal breaks in leukemic cells of miniature swine following chronic oral exposure to $^{90}SrCl_2$ is consistent with this idea (Clarke et al. 1972; Howard 1970). However, the specific genes involved in radiostrontium-induced malignancies have not been identified. Because of strontium's chemical properties, which determine its distribution in the body, exposure to sufficient radiostrontium results in an increased risk of malignancy for particular tissues. In dogs, acute inhalation of insoluble ^{90}Sr particles that lodged in the lungs resulted in chronic radiation exposure to the lungs, leading to pulmonary hemangiomas and carcinomas of pulmonary epithelia (Snipes et al. 1979). Other tissues were subsequently affected as the radioactive particles were cleared from the lungs. Following acute inhalation of soluble $^{90}SrCl_2$ aerosols, some dogs developed carcinomas of nasal airway tissues, probably resulting from irradiation of these tissues from the ^{90}Sr bound to the underlying bone (Gillett et al. 1987b). Following oral or inhalation exposures, absorbed ^{90}Sr was distributed to bone, from which it irradiated the surrounding tissues and induced various kinds of osteosarcomas, as well as malignancies of hematopoietic tissues in bone marrow (see Section 3.3.2.7).

Induction of Delayed Fibrosis Following External Exposure. A single high-dose external exposure to beta radiation can elicit acute epidermal reactions, late connective tissue damage, and carcinogenesis in

murine skin, as was demonstrated in experiments that used ^{90}Sr as a convenient beta source (Randall and Coggle 1996; see Section 3.3.3.7). A biochemical change that is associated with both acute and late effects is the enhanced expression of mRNA and protein for transforming growth factor beta 1 (TGF-beta l, Randall and Coggle 1995, 1996). Following an acute exposure to beta radiation from a ^{90}Sr source that is sufficient to generate moist desquamation, CBA/ca mouse skin exhibited two separate peaks of TGF-beta l expression (Randall and Coggle 1996). The first, occurring within the first few weeks after exposure, coincided with a period of epithelial hyperplasia that occurred during and after the phase of re-epithelialization. TGF-beta l expression declined to a low at 3 months postexposure, but then rose to another peak at about 9 months. Expression was especially high in the fibrotic dermis, which was also the site of skin tumors that appeared at about 9 months. TGF-beta l expression in tumors was elevated by 1.8 to 87 times the level in unirradiated control skin from the same animal. The implication of this study is that sustained high expression of transforming growth factor-betal may drive the progressive fibrosis and, possibly, contribute to malignancy following radiation damage. Another study from this laboratory indicates that there may be genetic differences in the control of TGF-beta l expression, and therefore, susceptibility to long-term effects of radiation damage (Randall and Coggle 1995).

3.6.3 Animal-to-Human Extrapolations

The toxic effects of stable and radioactive strontium have been similar in all species studied. However, as mentioned in Section 3.6.2, adult rats are not an optimal model for bone effects in adult humans because of the lack of a Haversian (bone remodeling) system in the rat and because of the persistence of the epiphyseal cartilaginous plate into adulthood (Leininger and Riley 1990). Because the epiphyseal cartilage persists, the long bones of rats continue to lengthen during adulthood, and therefore, the rates of incorporation of strontium will be proportionally higher. This will make adult rats more susceptible to adverse effects of both stable and radioactive strontium. This caveat does not apply to young rats, which are comparable to the young of other species. In general, rodents are not optimal models for radiostrontium effects because their small size ensures that most of their tissues will be within the effective range of beta emissions from radiostrontium bound to bone. Larger laboratory animals, such as dogs or non-human primates, avoid the problems of both radiation scatter to adjacent tissues and closure of the epiphysis as they become adults.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997c). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruptive effects in humans resulting from inhalation, oral, or dermal exposure to stable or radioactive strontium. Stable strontium, as an analog to calcium, is unlikely to cause endocrine disruption at normal levels of exposure. Endocrine glands, such as the pituitary, that are in close association with bone could potentially be damaged by irradiation from radioactive strontium incorporated into bone. For example, increases in tumors of the pituitary and

ovaries were observed in rats following gestational exposure to injected ^{90}Sr (Rönnbäck and Nilssen 1982; Schmahl and Kollmer 1981; Schmahl et al. 1979; Section 3.4.5.7). However, endocrine function was not tested in these studies. Ingested radioactive strontium had no effect on reproductive function in animals, suggesting that it did not affect reproductive hormones to an obvious degree (Clarke et al. 1972; Finkel et al. 1960). However, no study has specifically investigated the endocrine system.

3.8 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 resulting from 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. Exposures of children are discussed in Section 6.6 Exposures of Children.

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, 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 prenatal and postnatal 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. 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 et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The ubiquitous nature of stable strontium in soils and water supplies, and the chemical similarity of strontium to calcium, ensure that strontium will unavoidably be incorporated into the human body to some degree. Because of the requirement for high calcium intake during the period of bone development, the absorption and retention of strontium is higher in children than in adults; an ICRP (1993) model postulates that the fractional gastrointestinal absorption of strontium by infants (up to 12 months) is double that of adults (see Sections 3.5.1.2 and 3.5.5). Consequently, children are more at risk than adults from exposures to excess stable strontium or radioactive strontium.

Stable Strontium. A Turkish epidemiological study indicated that children with probable deficient vitamin D status (from insufficient exposure to sunlight) and diets low in calcium and animal protein were more likely to develop rickets as a result of exposure to excess dietary strontium (Özgür et al. 1996). The rachitic signs of craniotabes, rachitic rosary, bulging at the wrist, genu valgus, genu varus, and delayed closure of the fontanelles represented biomarkers of effect in children exposed to excess strontium. This study is consistent with numerous animal studies that demonstrated abnormal skeletal development (i.e., rickets) in young animals exposed to sufficiently high levels of dietary strontium (Kshirsagar 1976; Matsumoto 1976; Morohashi et al. 1994; Reinholt et al. 1985; Storey 1961, 1962; Svensson et al. 1985,

1987). Young rats may be sensitive to levels of ingested strontium that have no effect on adults (Storey 1961).

Children or young animals are likely to be more sensitive than adults to excess strontium, in part, because the rates of intestinal strontium absorption may be higher, although this has not been consistently demonstrated in humans (see Section 3.5.1.2 and Table 3-7). The ICRP (1993) biokinetic model for strontium assumes that the fraction of ingested strontium that is absorbed decreases from 0.6 in infancy to 0.3 in adulthood (see Section 3.5.5); some models assume the absorbed dose may be 8 times higher in infants compared to adults (NCRP 1991). These estimates are consistent with rat studies in which rates of strontium absorption were much higher (4–8 times) in weanlings compared to adults (Forbes and Reina 1972; Harrison et al. 1966b). This age-dependent difference in absorption may be partly explained by the duodenal level of vitamin-D-dependent calbindin D protein (a calcium-binding protein involved in absorption), which is much lower in old rats than in young rats (Armbrecht et al. 1979). Armbrecht et al. (1998) have demonstrated that the translation of calbindin D-9k mRNA into protein declines in the rat duodenum with age and this would be expected to reduce the rates of intestinal absorption of calcium and strontium in older animals.

Children are particularly vulnerable to excess strontium because the immature skeleton has a high rate of bone remodeling, and strontium adversely affects bone development in several ways, as demonstrated in animal studies. In chickens and rats, excess strontium suppresses the activation of vitamin D_3 in the kidney, which severely reduces the expression of calbindin D mRNA and the translation of calbindin D protein in the duodenum (Armbrecht et al. 1979, 1998; Omdahl and DeLuca 1972). As a result, duodenal absorption of calcium is reduced. Strontium also binds directly to hydroxyapatite crystals, which may interfere with the normal crystalline structure of bone in rats (Storey 1961). In addition, excess strontium may prevent the normal maturation of chondrocytes in the epiphyseal plates of long bones of rats (Matsumoto 1976). Excess strontium apparently interferes with the mineralization of complexed acidic phospholipids that is thought to help initiate the formation of hydroxyapatite crystals in developing bone (Neufeld and Boskey 1994). As a result, affected bone contains an excess of complexed acidic phospholipid and a significantly lower ash weight. This finding is consistent with the reduced rate of matrix vesicle degradation observed by Reinholt et al. (1984) in rachitic cartilage in strontium-treated rats.

The placenta does not accumulate strontium nor does it prevent transfer of strontium to the fetus following maternal exposure (see Section 3.5.2.2). However, no studies were located that addressed

developmental effects following maternal exposure to stable strontium in humans or animals. Stable strontium is also transferred to nursing infants through breast milk of exposed mothers at a ratio of approximately 0.24 µg strontium/mg Ca (Harrison et al. 1965). These levels are unlikely to be sufficiently high to perturb bone development in the fetus. Strontium stored in maternal bone because of prior exposure can be mobilized during pregnancy or lactation, resulting in fetal or infant exposure (Tolstykh et al. 1998).

Alginates, carbohydrates rich in guluronic acid, have been found to reduce peak exposure to strontium (see Section 3.12.1). Sutton et al. (1971a) showed that gastrointestinal absorption of stable ^{84}Sr was reduced 4-fold in children who were simultaneously given 10% sodium alginate-97% guluronic acid. Exposure to sunlight to enhance vitamin D status and diets with adequate calcium, phosphorus and protein may be considered to some degree protective against the effects of stable strontium (see Section 3.12).

Radioactive Strontium. During the period of above-ground nuclear weapons testing, the possible effects in children resulting from exposure to ^{90}Sr in radioactive fallout was a matter of concern. However, no studies have been able to identify unequivocally any increase in infant mortality, childhood cancers, or genetic damage in humans that could be attributed to oral or inhalation exposure to ^{90}Sr in fallout (NCRP 1991; Shaw and Smith 1970). In the Techa River populations that received higher oral doses of radiation, including radiostrontium, individuals who were exposed as teenagers exhibited a significantly higher frequency of stable chromosomal translocations compared to individuals who were exposed as adults (Bauchinger et al. 1998). Adverse pregnancy outcomes (mortality from developmental anomalies, chromosomal anomalies, labor complications, and other unspecified perinatal conditions) were elevated in the progeny of exposed individuals from the Techa River cohort, 60% of whom were exposed to radiation as teenagers (Kossenko et al. 1994). However, Kossenko et al. (1994) calculated that relatively high radiation doses (20–480 rem or 0.2–4.8 Sv) to the parental gonad would be required to double the incidences of stillbirths, miscarriages, early neonatal mortality, or lethal developmental effects. (Note that the gonadal radiation doses may have primarily been caused by exposure to external gamma radiation [Akleyev et al. 1995]). No increase in cancer incidence was observed among the progeny of the exposed Techa River population (Kossenko 1996). Dermal effects (slight dermal atrophy, telangectiasis, and pigmentation changes) were reported as delayed reactions to superficial ^{90}Sr treatments for facial hemangiomas in adults and children (Bekerus 1970). However, this study did not compare the relative sensitivity of children and adults.

It would not be expected that the immediate consequences of radioactive strontium exposure would differ in children and adults at the cellular level; that is, the initial damage to proteins and nucleic acids caused by ionizing radiation would be the same. Thus, children and adults might be expected to have similar effects following exposure to solid radiostrontium sources apposed to the skin or to insoluble particles of radiostrontium lodged in the lungs. However, as discussed in Appendix Section D.4.1, ionizing radiation is more damaging to actively mitotic cells than to differentiated postmitotic cells, largely because genetic lesions become permanent when cell division occurs before repair can occur. Since children have proportionally more mitotic cells than adults, the biological effect of radiation exposure in children would be expected to be proportionally more severe. Other developmental aspects contribute to the higher potential vulnerability of children to radiation effects. One is the higher rate of gastrointestinal absorption in children, as discussed for Stable Strontium, above. In addition, animal studies indicate that the young are more vulnerable than adults to inhalation or oral exposures to radioactive strontium in soluble form, because of higher rates of retention in the developing skeleton (see Stable Strontium section above). Thus, a given absorbed dose of soluble radiostrontium will have a longer biological half-life in young animals compared to adults, leading to higher cumulative radiation doses to bone and surrounding soft tissues and more severe adverse effects (see Section 3.3). Examples of this age-related difference in severity are discussed under Section 3.2.2.2 Musculoskeletal Effects (especially Storey 1961, the basis for the intermediate oral MRL) and Section 3.3.2.2 Hematological Effects (Cragle et al. 1969), and Section 3.3.2.6 Reproductive Effects (Clarke et al. 1970). Young animals exhibit the same types of effects as adults (e.g., malignancies), in addition to other effects specific to their developmental stage. For example, radioactive strontium disturbed osteogenesis of long bones in young rats by damaging the epiphyseal cartilaginous discs, and the vasculature that supports resorption (Casarett et al. 1962). In weanling rats, irradiation of the marrow prevented its invasion of metaphyseal cartilage, thereby causing cartilage to resume active proliferation, rather than undergo transformation into bone. Because of disruption of these processes, cartilage and fibrous marrow were sometimes incorporated into cortical bone, resulting in weakness or fracture. For all species studied, a long-term effect of ^{90}Sr incorporation in young animals or *in utero* was a higher incidence of bone-associated cancers compared to animals exposed as adults (Clarke et al. 1972; Finkel et al. 1960; White et al. 1993). Size differences may contribute to the possible higher vulnerability of children to bone marrow effects from retained radiostrontium. Since bone marrow cavities in children have smaller diameters, a larger proportion of the hemopoietic bone marrow is within the approximate centimeter range of beta radiation emitted from radiostrontium bound to the endochondral surface.

There are two theoretical ways in which the fetus might be exposed to radiation from the decay of radioactive strontium: from transfer of strontium across the placenta or from proximity to radiation emitted from the maternal body. Placental transfer of radioactive strontium to the fetus has been demonstrated in humans (Sikov et al. 1991, Stather et al. 1992) and animals (rodent: Onyskowova and Josifko 1985, Taylor and Bligh 1992; pig: Palmer et al. 1969). Studies of residents of the Techa River who were exposed to strontium as a result of an accident at a plutonium production plant provide evidence that fetal exposures can result from previous maternal exposures. The fetal:maternal strontium concentration ratio in four subjects who were exposed prior to pregnancy varied from 0.012 to 0.24, with the higher values associated with maternal exposures that occurred during adulthood and lower values associated with maternal exposures during childhood or adolescence (Tolstykh et al. 1998). A dosimetry study in minipigs determined that exposure of the fetal thymus (ages 55–110 days of gestation) to radiostrontium (^{90}Sr–^{90}Y) is related to the amount that is incorporated by the fetus after placental transfer; no appreciable radiation reached the thymus from radiostrontium in the maternal uterine wall (Palmer et al. 1969). Palmer et al. (1969) indicated that results might vary for other organs, for younger fetuses (which may be relatively closer to the maternal uterine wall or pelvic bone), or for single fetuses compared to multiple fetuses (as in the pig). As discussed in Section 4.2, strontium isotopes and their transformation product isotopes differ with respect to their emission energies; this factor is another variable that will determine whether the fetus is subject to radiation from the maternal body.

Animal studies demonstrate that the developmental consequences of injecting pregnant females with radioactive strontium are qualitatively different depending on the gestational day of administration (Finkel and Biskis 1969; Finkel et al. 1972; Hopkins et al. 1967). This is partly related to temporal differences in the onset of osteogenic activity and calcification in different parts of the skeleton. For example, the increase in calcification of the basioccipital and sphenoid bones of the skull occurring by gestational day 18 of the rat probably contributed to the development of pituitary gland tumors after an injection of ^{90}Sr was administered that day (Schmahl and Kollmer 1981; Schmahl et al. 1979). A single injection administered to pregnant mice late in gestation transiently affected fertility of male offspring by suppressing spermatocyte maturation, but severely depressed oocyte maturation of the female offspring (De Rooij and Rönnbäck 1989; Nilsson and Henricson 1969; Rönnbäck 1979, 1980, 1981a, 1981b).

Radioactive strontium, like stable strontium, can be transferred to infants through breast milk of exposed mothers (Harrison et al. 1965). Rönnbäck (1981a) demonstrated that the numbers of oocytes (all stages) in the ovary was reduced in neonatal mice that were exposed to radioactive strontium in the milk of surrogate females that had been given high doses by injection.

Various methods for reducing the body burden and toxic effect of radioactive strontium have been investigated (see Section 3.12). Only the administration of alginates high in guluronic acid, described in the previous section, has been validated in children (Sutton et al. 1971a). A single oral dose of aluminum phosphate antacid gel taken soon after exposure is a recommended treatment for reducing absorption of ingested strontium (Ellenhorn et al. 1997; Haddad et al. 1998). This would be a suitable treatment for children as long as the dosage recommendations were followed, since excess ingestion of aluminum phosphate can cause rickets (Chines and Pacifici 1990; Pivnick et al. 1995). A diet high in calcium would tend to reduce the incorporation of radioactive strontium into bone (Steinbach 1968).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to strontium are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of

tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by strontium are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11 "Populations That Are Unusually Susceptible".

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Strontium

The biomarkers to quantify exposure to stable or radioactive strontium are similar in children and adults.

Stable strontium is ubiquitous in the diet and can be measured in urine, blood and feces by a number of methods outlined in Section 7.1. After exposure, approximately 99% of the absorbed strontium that is retained is found in bone and connective tissues (Schroeder et al. 1972). Normal background levels of strontium were measured by emission spectrography in cadaver tissue from 168 American subjects (Tipton 1981; Tipton and Cook 1963). Average strontium levels in human tissues expressed as ppm ash were as follows: rib bone 110 ppm, vertebra 100 ppm, aorta 33 ppm, ileum 25 ppm, duodenum 11 ppm, lung 8.2 ppm, kidney 5.2, heart 2.6 ppm, and liver 1.6 ppm. In a small group of adult males, the mean strontium concentration in plasma was 29 μg/L (Sutton et al. 1971b).

Soluble radioactive strontium can be detected in urine, blood, or feces by liquid scintillation counting. Whole body counters (or chest counters for inhalation exposures) can measure internal radioactive strontium deposited in bone following high level exposures (see Section 7.1.1). Children tend to incorporate strontium more homogenously throughout bone than is the case for adults.

3.9.2 Biomarkers Used to Characterize Effects Caused by Strontium

Deformities of bone in response to excess strontium can be detected by radiography. Exposure to excess stable strontium may cause specific abnormalities in bone calcification that can lead to obvious bone deformities, particularly in the young. Such 'rachitic' signs in children include craniotabes, rachitic rosary, conspicuous bulging at the wrist, genu valgus, genu varus, and delayed closure of the fontanelles (Özgür et al. 1996). However, excess exposure to other metals, such as aluminum (Bhattacharyya et al. 1995; Carmichael et al. 1984; Chines and Pacifici 1990; Pivnick et al. 1995; Woodson 1998) or deficiencies in calcium, vitamin D, and/or phosphate can generate the same effects. Thus, this is not a specific biomarker for strontium, but can be confirmatory. Although bone biopsies can measure strontium chemically, these tests are not warranted because of the relatively high risk/benefit ratio.

Exposure to radioactive strontium may result in lowered blood cell counts, which can be detected using standard clinical laboratory methods. However, exposure to other sources of ionizing radiation has similar effects. Sufficiently high exposures to radioactive strontium can result in genetic damage to tissues adjacent to bone. Recently, Sutherland et al. (2000a, 2000b) developed a molecular biological strategy to identify clustered lesions in DNA resulting from *in vitro* cellular exposure to gamma radiation. It is possible that this technique might be adapted to evaluate genetic damage in blood cells following exposure to radioactive strontium, although, again, it would not be specific for radiostrontium, but rather for ionizing radiation. It is uncertain whether the technique would be applicable for the chronic exposures characteristic of absorbed radiostrontium compared to the acute high-dose exposures for which it was designed.

3.10 INTERACTIONS WITH OTHER CHEMICALS

Several agents reduce the absorption or retention of strontium, reducing its toxic effects (see Section 3.12).

Calcium. Strontium has chemical properties similar to calcium, but is less efficient than calcium in most biological processes. Calcium and strontium appear to compete for the same transporter elements in the intestine (Bianchi et al. 1999; Blumsohn et al. 1994; Milsom et al. 1987; Reid et al. 1986; Sips et al. 1994), but calcium is preferentially absorbed. Co-administration strontium and calcium reduces the

uptake of strontium and also reduces skeletal retention of strontium (Palmer et al. 1958; Roushdy et al. 1980, 1981; Steinbach 1968).

Anions. Oral administration of phosphate, as aluminum phosphate antacid gel, reduces the gastrointestinal absorption of strontium by increasing its excretion in feces (Carr and Nolan 1968; Keslev et al. 1972; Spencer et al. 1969a, 1969b). Oral administration of sulfates at the same time as strontium reduces its retention in the skeleton (Volf 1964). These agents are discussed in Section 3.12.1.

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to strontium than will most persons exposed to the same level of strontium in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of strontium, or compromised function of organs affected by strontium. Populations who are at greater risk due to their unusually high exposure to strontium are discussed in Section 6.7, Populations With Potentially High Exposures.

In general, children, who are in the stage of active bone synthesis and growth, are more vulnerable to adverse effects of strontium. A more detailed discussion of children's susceptibility can be found in Section 3.8. The following discussion is limited to other individual variations or health conditions that may modify the usual effects of strontium.

Protein Deficiency and Ethanol Consumption. Protein-deficient diets may increase the adverse effects of exposure to excess stable strontium or to radioactive strontium, by reducing clearance and increasing incorporation into bone. A metabolic experiment in adult male Wistar rats showed that consumption of a protein-deficient diet increased the intestinal absorption of dietary strontium and its incorporation into bone, while reducing fecal and urinary excretion of strontium (Gonzales-Reimers et al. 1999). When rats were given ethanol in addition to the protein-deficient diet, incorporation of strontium into bone was significantly enhanced, although ethanol given with a protein-normal diet tended to reduce strontium incorporation through its diuretic effects.

Renal Disorders. Patients with chronic kidney failure may be more susceptible to excess strontium than the general population, because of a reduced ability to excrete strontium and retain calcium (Apostolidis et al. 1998). In such patients, plasma levels of strontium were found to be 60% higher compared to

controls. In a variety of studies, uremic patients on dialysis were found to have significantly higher levels of strontium in serum, muscle, and brain tissue compared to normal undialized controls (Alfrey et al. 1975; Couttenye et al. 1999; D'Haese and De Broe 1996; D'Haese et al. 1999, 2000; Krachler et al. 2000; Schrooten et al. 1999). Although the high level of strontium in serum in uremic patients was correlated with the high level of strontium in the local tap water, it is also possible that uremic patients may have reduced rates of strontium excretion.

Paget's Disease (osteitis deformans). Patients with Paget's disease (osteitis deformans) had a higher than normal retention rate following administration of ^{85}Sr (Tothill et al. 1983). Part-body retention measurements demonstrated that diseased bone had relatively higher uptakes of strontium compared to undiseased bone. Pagetic bone contains a higher proportion of small mineral crystals with greater surface area, which accounts for its increased ability to accumulate strontium. Reflecting the high degree of osteoclast activity in Paget's disease, diseased bone had an increased turnover of ^{85}Sr, compared to undiseased bone in the same patient. Since bone metabolism is locally accelerated in persons with this disease, they are likely to develop higher body burdens of radioactive strontium than healthy adults.

Rheumatoid Arthritis or Seronegative Spondarthritis. Patients with active rheumatoid arthritis or seronegative spondarthritis were found to have significantly higher levels of strontium and calcium in their granulocytes (Hällgren et al. 1984). The strontium overload was thought to be linked to the degree of inflammation and was positively related to serum levels of the acute-phase protein haptoglobin; corticosteroid therapy differentially reduced the strontium content of granulocytes compared to calcium. It is not known whether granulocytes in persons with active disease would take up relatively more radiostrontium from plasma, and therefore incur more damage, than would be the case for otherwise healthy individuals under an identical exposure scenario.

Diabetes. Persons with diabetes may be more vulnerable to adverse effects from dermally-applied radioactive strontium. Thinning of the sclera developed in a diabetic patient who had been treated for pterygium with a single dose (1,700–1,800 rad; 17–18 Gy) of ^{90}Sr (Wesberry and Wesberry 1993; see Section 3.3.3.2). This reaction was not observed in 170 other eyes treated at that dose level; however, the authors did not state whether other diabetics were in the group that was unaffected. Conversely, in rats made diabetic by injection of streptozotocin, the absorption of strontium in the duodenum was significantly reduced, which would appear to be protective (Miller and Schedl 1976).

Genetic Polymorphisms. Polymorphisms in genes that may affect rates of strontium (calcium) absorption and bone mineralization are currently under investigation. In a study of postmenopausal women with osteoporosis, polymorphisms of vitamin D receptor genes apparently caused a 40% variation in the rate of strontium absorption (Gennari et al. 1997); however, another study found no association between vitamin D receptor polymorphisms and bone mineral density in osteoporotic women (Poggi et al. 1999). Similarly, 3'-end region polymorphisms of the vitamin D receptor were found to have no effect on enteral strontium absorption or bone mineral density in patients with calcium kidney stone disease (Vezzoli et al. 2002). Insulin-like growth factor (IGF-I) is correlated with age-related changes in strontium absorption in men (Fatayerji et al. 2000), but polymorphisms have not been evaluated. Other candidate genes that may affect bone mineralization include the parathyroid hormone receptor 1, the estradiol receptor, collagen type I alpha 1, transforming growth factor-beta 1, interleukin-6, calcitonin receptor, alpha2-HS-glycoprotein, osteocalcin, calcium-sensing receptor, interleukin-1 receptor antagonist, beta-3-adrenergic receptor, apolipoprotein E, glucocorticoid receptor, and epidermal growth factor (Audi et al. 1999; Duncan et al. 1999). The relative contribution of these factors on bone mineralization has yet to be clarified and whether any polymorphisms increase susceptibility to adverse effects of strontium remains to be determined.

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to strontium. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to strontium. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to strontium:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams & Wilkins, 1682–1723.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia, PA: W.B. Saunders, 413–425.

Viccellio P, ed. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven, 991–996.

3.12.1 Reducing Peak Absorption Following Exposure

Human exposure to strontium and its compounds occurs primarily by inhalation and ingestion, since absorption is poor following dermal contact. Current suggestions for reducing absorption of radiostrontium include ingestion of antacids containing aluminum phosphate (Ellenhorn et al. 1997; Haddad et al. 1998). Treatment is most effective when it is initiated within 2 hours of exposure.

The threat of nuclear fallout from atomic weapons testing was the impetus for a large number of studies that investigated methods to prevent absorption of radiostrontium, while not adversely affecting the absorption of calcium. Reasonably effective strategies have included alginates, aluminum phosphate, and sulfates. Less effective or less practical strategies have included cold, diet, dietary fiber, flavones, and stable strontium.

Alginates. Alginates are carbohydrates derived from seaweed that have been found to reduce the absorption of strontium in humans and animals, without significantly affecting the absorption of calcium. When 10% sodium alginate-97% guluronic acid was given orally along with the stable marker $^{84}SrCl_2$ to children (ages 2.5–10 years), plasma ^{84}Sr was reduced by 75% and urinary excretion of the tracer was reduced 72% (Sutton et al. 1971a). The authors concluded that absorption was reduced 4-fold. In adults, sodium alginate extracts administered as a liquid or in bread, reduced strontium absorption by 50% in humans and 3-fold in rats (Gong et al. 1991). Alginates with a high guluronic acid/mannuronic acid ratio were found to be more effective in humans and rats (Carr and Nolan 1968; Gong et al. 1991). Sodium alginate administered orally to rats effectively reduced the whole body retention of ^{85}strontium that had been administered intratracheally (Naményi et al. 1986). Calcium alginate added to the diet of female goats reduced the transfer of ^{85}strontium to milk, which was attributed to a reduction in strontium absorption (Beresford et al. 1999). In rats given ^{89}Sr and ^{45}Ca by gavage, alginate treatment, particularly in combination with stable calcium, differentially increased the fecal excretion of ^{89}Sr and reduced the skeletal retention of ^{89}Sr (Light et al. 1970a).

Aluminum Phosphate Antacid Gel. Aluminum phosphate antacid gels, administered just prior to or shortly after oral strontium exposure, have been shown to reduce absorption of strontium by increasing its excretion in feces in humans (Spencer et al. 1969a, 1969b), rats (Carr and Nolan 1968), and mice (Keslev et al. 1972). A practical advantage of this treatment is that the gels are readily available as over-the-counter pharmaceuticals. In elderly men who had been maintained on a low calcium diet for several weeks, oral administration of an antacid gel just prior to oral $^{85}Sr/^{45}Ca$ exposure reduced plasma

radiostrontium levels by 88%, but reduced radiocalcium levels by only 38% (Spencer et al. 1969a). In the same study group, antacid treatment reduced strontium absorption by 57% when given 0.5 hours after exposure, but by only 43%, 1 hour after exposure (Spencer et al. 1969b). In similar studies on rats fed antacid for several days prior to exposure, the absorption of strontium was reduced by 83%, whereas there was no effect on the absorption of calcium (Carr and Nolan 1968). In mice, an aluminum phosphate gel reduced the absorption of strontium by about 13-fold and of calcium by about 3-fold (Keslev et al. 1972).

Sulfates. In rats orally exposed to radiostrontium and monitored on day 2, oral administration of barium sulfate in combination with sodium sulfate or magnesium sulfate reduced radiostrontium retention in the femur by nearly 80% (Volf 1964). Treatment was effective if given within 10 minutes of exposure, but not if delayed more than 80 minutes. Strontium sulfate was less effective, reducing radiostrontium retention by only 30%. Volf (1964) did not determine whether the effectiveness of the barium sulfate combination therapy was a result of increased diuresis or decreased bioavailability by means of adsorption to radiostrontium in the intestine.

The following treatments have been shown to be less effective or less practical.

Diet or Dietary Fiber. A pulverized solid diet administered to rat sucklings over 8 hours resulted in 10–20% less whole body retention of ^{85}Sr (reduced absorption) than cow milk (Kostial et al. 1981b, 1984). Supplementing cow milk with trace elements did not improve its effectiveness, ruling out the possibility that trace elements in the food competitively inhibited intracellular transport of ingested strontium. Rather, the authors suggested that the solid diet contained ligands for strontium that reduced the amount of strontium available for transport. Another study demonstrated that the inclusion of cellulose fiber into the diet of suckling rats decreased the retention of simultaneously administered $^{85}Sr/^{45}Ca$ by 20% (Momčilovič and Gruden 1981). However, cellulose fiber was less satisfactory than alginates, both in effectiveness and in the lack of discrimination between strontium and calcium.

Flavones. In rats given doses of flavone (Ipriflavone, 7-isopropyl-isoflavone, or Morin, 2',2,4',5,7-pentahydroxy-flavone) for 3 weeks prior to acute oral exposure to radiostrontium, the whole body retention of radiostrontium was reduced by 50 and 30%, respectively, after 1 month (Gachályi et al. 1988). Similar experiments on pregnant rats demonstrated that both flavones reduced fetal uptake of radiostrontium administered to dams on gestational days 17/18 and 19/20. No studies were located that demonstrated the usefulness of flavones for emergency situations, rather than as pretreatments.

Stable Strontium. In weanling rats previously given varying amounts of strontium lactate in the diet, 4 or 6% strontium lowered the retention of injected radiostrontium to a greater extent than the retention of injected radiocalcium (Teree et al. 1965). The disadvantage of this treatment is the adverse effect on bone development caused by excess stable strontium.

3.12.2 Reducing Body Burden

Absorption of strontium can vary with the chemical form of the compound and its solubility. Those strontium compounds that are readily absorbed following inhalation or oral exposure are rapidly distributed throughout the body (see Section 3.5). Because of its similarity to calcium, strontium entering the circulation preferentially accumulates in bone. Methods for reducing the body burden of radiostrontium that have been tested in animals include calcium, chelators (with variable results), hemodialysis, and magnesium sulfate. Exposure to cold temperatures, use of the few pharmacological agents that have been tested, and use of stable strontium are less satisfactory treatments.

Calcium. In human patients with osteoporosis who were injected with tracer doses of $^{85}SrCl_2$, intravenous infusions of calcium gluconate significantly increased urinary excretion of strontium, but had no effect on fecal excretion (Spencer et al. 1967d). This effect was attributed to the decreased renal tubular reabsorption of calcium under these conditions. Calcium gluconate was more effective than magnesium chloride tested in the same study. A 10-day series of injections with a combination of calcium and calciferol reduced the retention of ^{90}Sr in rabbits by 70%, if the treatments started as soon as 24 hours after exposure (George et al. 1979). If treatments were delayed 96 hours, the removal of strontium was reduced by 50%. Slightly less effective treatments included calcium alone, sodium citrate, or a combination of calcium and magnesium, which reduced strontium retention by 40, 30, and 20%, respectively. A 3-week diet high in calcium and low in phosphorus, initiated 24 hours after injection of ^{90}Sr into rats, significantly reduced the incorporation of the isotope into bone (Steinbach 1968). In rats, pretreatment with diets rich or adequate in calcium tend to result in lower accumulations of radiostrontium in bone following exposure than diets poor in calcium (Palmer et al. 1958; Roushdy et al. 1980, 1981). However, administration of a high-calcium diet to rats following a month-long parenteral exposure to radiostrontium, only slightly reduced the strontium content of the femur after 65 days (Ray et al. 1956).

Chelators. Chelators are not effective once strontium has become incorporated into hydroxyapatite. A variety of chelators have been tested in rodents, with variable results. In general, chelators did not

successfully increase the excretion of radiostrontium, if administered 6 or 24 hours after exposure (e.g., Llobet et al. 1991a, 1991b, 1992a). In tests on rats, the cryptator hexaoxa-diamine macrobicycle was effective when given simultaneously with radiostrontium (Müller 1970). The aza crown ether 2NaCa Kryptofix 22 was effective in tests on mice and rats when administered intravenously or intratracheally within 1 hour of exposure to radiostrontium (Varga et al. 1994). Other aza crown ethers and other chelators have been tested on mice following parenteral exposure to strontium, but their effectiveness has been so variable and no consistent conclusions can be drawn (Colomina et al. 1991; Llobet et al. 1992b; Ortega et al. 1989). For example, Na_2Ca EGTA (Na_2Ca ethylenglycol-bis-(β-amino-ethyl-ether)-N,N'-tetraacetic acid) increased fecal excretion of subcutaneously administered strontium (nitrate), but decreased urinary excretion to the same degree, and thus, there was no net change (Colomina et al. 1991).

Chelators that were not at all effective in rodent studies include monosodium glutamate, Tiron (4,5-dihydroxy-1,3-benzene-disulfonic acid), DMSA (2,3-dimercaptosuccinic acid), succinic acid, malic acid, $CaNa_2CTDA$ (cyclohexanediaminetetraacetic acid), and THPC, a cyclic derivative of EDTA (Kostial et al. 1979; Llobet et al. 1992b; Ortega et al. 1989).

The chelating agent, zirconium citrate, administered intraperitoneally in several injections soon after parenteral exposure to ^{90}Sr, significantly reduced the number of mice with bone tumors, reduced the multiplicity of tumors, and delayed the onset of tumors (Zander-Principati and Kuzma 1964). Measurements of external brehmsstrahlung emissions 10–12 months later demonstrated that mice treated with zirconium citrate had a reduced body burden of radiostrontium, which is the likely cause of the reduced tumor rate. One source of uncertainty regarding this study, despite the claims of low toxicity for zirconium citrate, is the unexplained reduction in lifespan in all the groups treated with the chelator.

Cold. In mice exposed to low temperature (9 °C), the rate of urinary excretion of a radiostrontium tracer was increased (Wedin 1972; Wedin et al. 1972). This was attributed to a specific effect of cold on the rate of diuresis. However, since the rate of calcium excretion was not measured in this study, but is also known to be increased by cold, the usefulness of this finding is not clear. Urinary excretion rates of radioactive strontium in mice intraperitoneally injected with ^{85}Sr were increased about 10% by transfer to 4 °C (Nilsson and Rönnbäck 1988).

Hemodialysis. Hemodialysis is only effective if administered soon after exposure to strontium. In 100-day-old calves injected with ^{85}Sr, a 12-hour hemodialysis session administered 4, 14, or 24 hours

later resulted in removal of only 14, 4, and 2.5% of the administered dose, respectively (Downey et al. 1964).

Magnesium. In human patients with osteoporosis who were injected with tracer doses of $^{85}SrCl_2$, intravenous infusions of magnesium chloride significantly increased urinary excretion of strontium, but had no effect on fecal excretion (Spencer et al. 1967a). Magnesium chloride was not as effective as calcium gluconate tested in the same study. Magnesium sulfate injected 10 minutes after $^{85}SrCl_2$ significantly reduced the body burden of strontium in rats, irrespective of the dietary calcium or vitamin D status (Roushdy et al. 1980, 1981).

Pharmacological Agents. Tests of the effectiveness of hormones or drugs in reducing the body burden of strontium have been disappointing. In rats, progesterone had no significant effect on radiostrontium retention, whereas estrogen actually increased the amount of ^{90}Sr in the femur (Steinbach 1968). In rabbits, the steroid prednislone, thyroxine, and the diuretic furosemide removed only about 30, 15, and 10%, respectively, of the administered dose of ^{90}Sr (George et al. 1979).

Phosphorus-reduced Diet. A diet low in phosphorus (0.017%, Ca/P ratio of 21.5) was most effective in mobilizing radiostrontium from the rat skeleton (Ray et al. 1956). Nearly 85% of the strontium incorporated into the femur was removed by the 50th day; only 0.24% of the injected dose remained in the femur. However, this diet caused serious adverse effects: minimal increase in body weight, delayed growth and narrowing of epiphyseal discs in the tibia, reduced ash weight of the femur, and poor health necessitating termination of the experiment. Consumption for 64 days of a diet 'subminimal' in phosphorus (0.21%, Ca/P ratio of 2.19) removed nearly 64% of the radiostrontium incorporated into the femur. Rats exhibited normal body weight gain and ash weight of the femur, but there were histopathological changes in the epiphyseal discs and trabeculae of the tibia. Although the low and 'subminimal' phosphorus diets were relatively effective in reducing the body burden of radiostrontium, the potential for adverse health effects from inadequate phosphorus intake reduces the value of this strategy.

Strontium-free Diet. In young rats maintained on a diet high in strontium for 28 days, returning to a normal diet low in strontium noticeably reversed the adverse effect on bone mineralization (Johnson et al. 1968). The reduced percentage of ash in bone began to show improvement after 2 weeks and was nearly normal after 5 weeks. In addition, the abnormal deposition of osteoid in vertebrae was repaired.

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

Hyperbaric oxygen therapy was successfully used to treat a case of scleral necrosis resulting from ^{90}Sr therapy following pterygiectomy (Green and Brannen 1995). Repeated hyperoxygenation enhanced neovascularization and regrowth of the scleral tissue that had become avascular and abnormally thin as a result of exposure to beta radiation.

In tests on irradiated skin of guinea pigs, anti-inflammatory compounds reduced the permeability of the dermal vasculature to plasma proteins by up to 30% (Song et al. 1968). However, since drug treatment was administered both before and after irradiation, this study is not definitive proof of the efficacy of these compounds.

3.13 ADEQUACY OF THE DATABASE

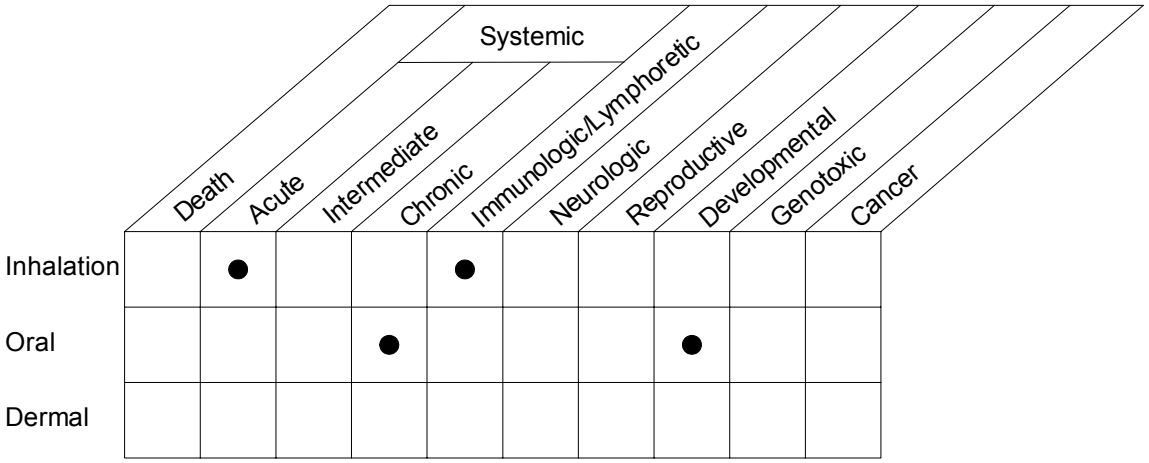
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of strontium is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of strontium.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

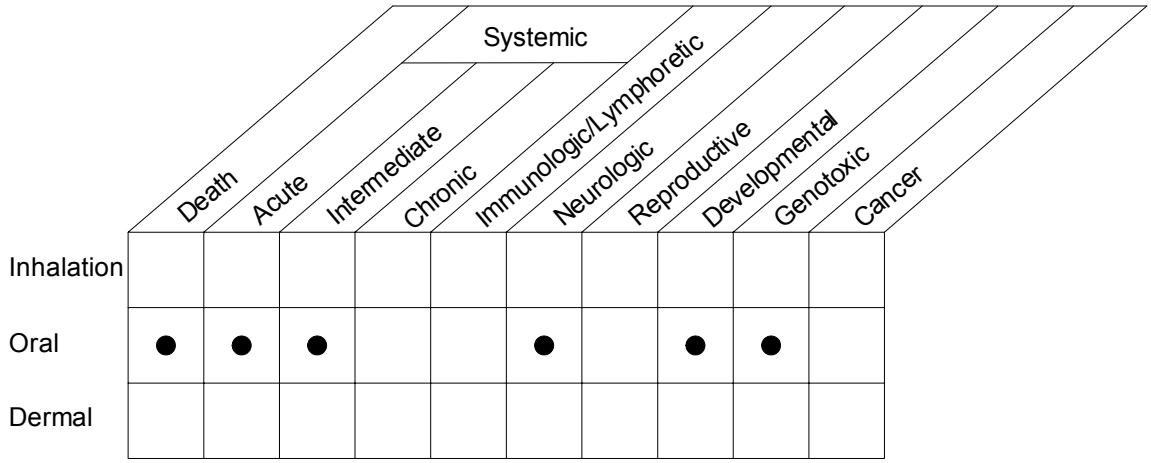
3.13.1 Existing Information on Health Effects of Strontium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals are summarized in Figure 3-9 for stable strontium and in Figure 3-10 for radioactive strontium. The purpose of these figures is to illustrate the existing information concerning the health effects of strontium. Each dot in the figure indicates that one or more studies provide information associated with that particular

Figure 3-9. Existing Information on Health Effects of Stable Strontium



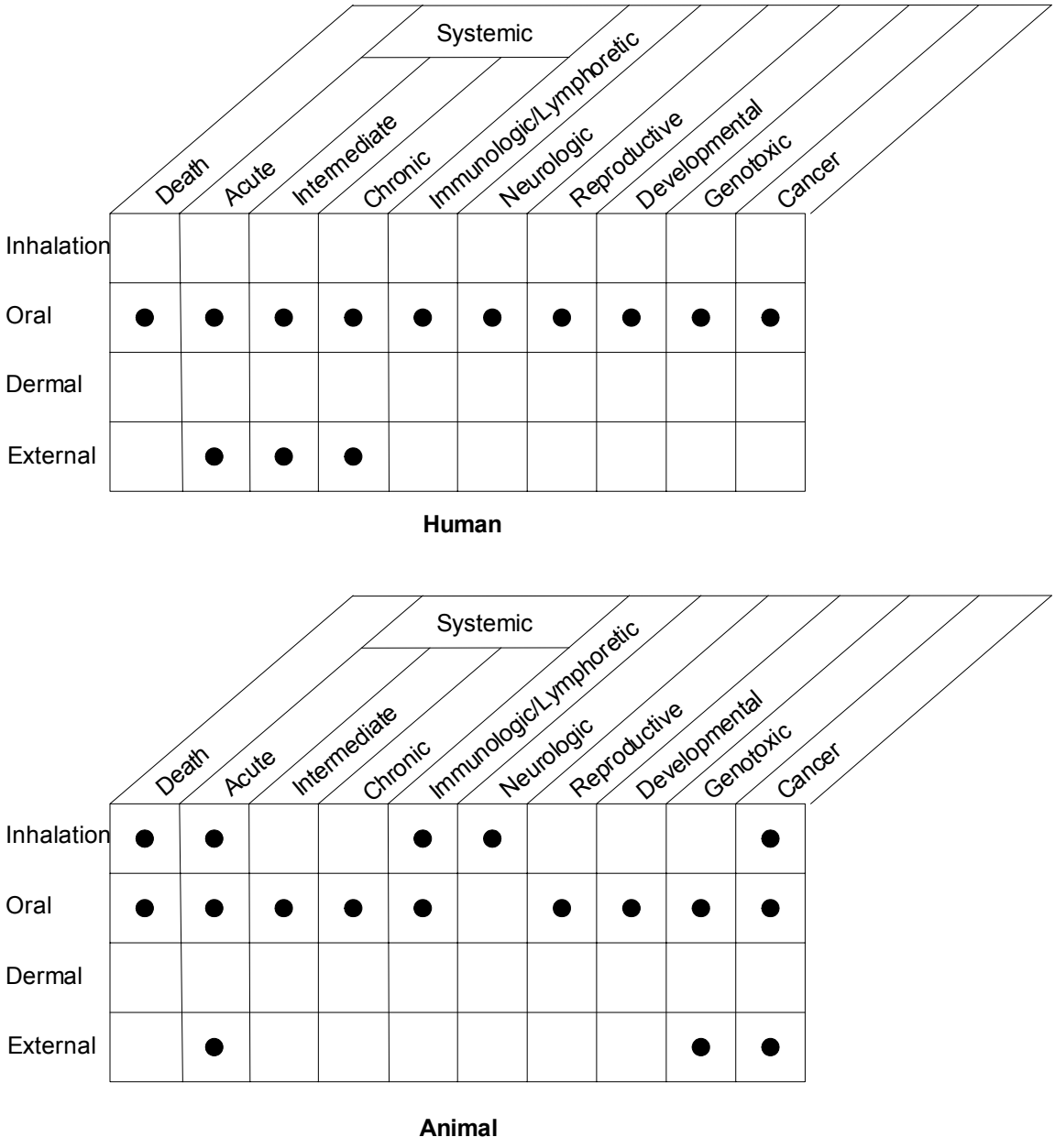
Human



Animal

● Existing Studies

Figure 3-10. Existing Information on Health Effects of Radioactive Strontium



effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

3.13.2 Identification of Data Needs

In the following discussion, the toxicity (carcinogenicity) of inhaled strontium chromate is omitted, since its adverse effects are attributed to hexavalent chromium (see Section 3.2.1.7). Unless otherwise stated, the proposed investigations refer to studies of health effects in animals.

Acute-Duration Exposure.

Stable Strontium. Information from injection and kinetic studies in humans and oral, inhalation, and injection studies in animals indicates that bone is the primary target tissue of absorbed stable strontium. The acute database is inadequate for deriving MRLs. A data need for an acute inhalation study is discussed under Data Needs for Immunotoxicity. Animal studies have shown that stable strontium is not toxic at low doses (Kroes et al. 1977). On the other hand, high oral doses of stable strontium can severely depress the serum levels of 1,25-dihydroxyvitamin D in rats within a week, which has an adverse effect on calcium absorption (Armbrecht et al. 1979, 1998). Of the two available acute oral toxicity studies, one employed ineffective doses, and the other used a single high dose (Kroes et al. 1977; Kshirsagar 1976).

Thus, there is a need for an acute-duration oral study that would enable an analysis of dose-response relationships with regard to strontium ingestion and skeletal effects. Consideration should be given to comparing the relative effects of different forms of strontium (e.g., strontium chloride, strontium carbonate, strontium phosphate), and different modes of delivery (in food, in water), since these factors probably affect the bioavailability of ingested strontium. In addition, such a study could provide a basis for investigating possible biomarkers of effect (by monitoring changes in the serum levels of vitamin D, 1,25-dihydroxyvitamin D, calcium, phosphorus, phosphatases, and other biomarkers) that could be used to characterize the early systemic response to strontium.

Radioactive Strontium. Acute-duration inhalation or oral administration of radioactive strontium caused adverse effects. No dermal studies were conducted. Rather, external studies used solid strontium apposed to the skin, which did not provide an opportunity for dermal absorption (Hoshino and Tanooka 1975; Randall and Coggle 1995; Song et al. 1968). In dogs, inhalation of relatively insoluble particles of radiostrontium resulted in prominent damage to pulmonary tissues (Benjamin et al. 1975, 1976c; Snipes et al. 1979). Inhalation or ingestion of soluble radiostrontium resulted in radiostrontium incorporation into bone and subsequent chronic radiation exposure of the surrounding tissues (inhalation: Gillett et al. 1987a, 1987b; oral: Casarett et al. 1962; Cragle et al. 1969). No inhalation or oral MRLs could be derived because the effects of exposure, even at the lowest levels, were serious. There is a need for an inhalation study using soluble strontium aerosols that would test a lower range of exposure levels than had previously been employed, primarily to assess the effects on the lymphocyte population; existing studies found chronic depression of lymphocyte numbers even at the lowest concentrations. Existing acute-duration oral studies are inadequate because either the study size was small and/or a single dose was used. There is a need for an acute oral multi-dose study, in particular, one comparing effects in young and adult animals, primarily for the purpose of relating genotoxicity to dosage. Dermal studies using strontium applied to the skin should be conducted to evaluate systemic effects that might occur following the kind of exposure that might occur in the vicinity of a hazardous waste site.

Intermediate-Duration Exposure.

Stable Strontium. An intermediate oral MRL was derived on the basis of a study that showed young rats were more susceptible to adverse skeletal effects (rickets) than adults (Storey 1961). A considerable number of studies support this finding (see Section 3.2.2.2 Musculoskeletal Effects). No intermediate inhalation study was located. The necessity for an intermediate inhalation study should be evaluated once the data from the proposed acute inhalation study are assessed. No intermediate dermal study was located, but given the low cytotoxicity of stable strontium, such a study does not seem necessary.

Radioactive Strontium. No intermediate-duration inhalation, oral, or dermal studies were located. There is a need for intermediate-duration inhalation and oral studies, using low levels of exposure, to help define the risk associated with longer-term exposures, such as may occur from radiostrontium releases at nuclear fuel reprocessing facilities or nuclear power plants into air, into drinking water, or settling onto croplands. The primary focus of these studies should be hematological and immunological effects. Some information is available in intermediate external studies, but in these, radiostrontium was not applied to the skin in a form that could be absorbed. Dermal studies need to be conducted to assess the systemic risks that children might incur by playing in the open after radiostrontium has settled on the ground.

Chronic-Duration Exposure and Cancer.

Stable Strontium. There were no adequate chronic-duration studies of stable strontium effects in humans or animals. In a review paper, Skoryna (1981a) briefly mentioned that oral administration of low doses of strontium had no adverse effect in rats over a 3-year period or over several generations, but provided no experimental details. A chronic-duration oral study would be useful for evaluating the long-term health effects of strontium ingestion. Some consideration should be given to comparing the effects of compounds having different chemical properties (e.g., strontium chloride, strontium carbonate, and strontium phosphate).

Although there are no chronic studies of stable strontium exposure, the rest of the database provides no evidence to suspect that stable strontium might be carcinogenic. It does not appear that a long-term carcinogenesis study would prove useful.

Radioactive Strontium. There is no chronic inhalation study for radioactive strontium. Such a study should be considered after an intermediate inhalation study is conducted, as a means of evaluating long-term exposure to low levels of radioactivity on the immune system. The Techa River cohort represents the major source of information regarding the health effects of chronic exposure to radiostrontium: suppression of hematopoiesis and immune function (Akleyev et al. 1995). Chronic oral administration of radioactive strontium has been shown to suppress hematopoiesis and lymphocyte function in animals (Dungworth et al. 1969; Howard 1970). Since these effects were observed at the lowest exposure levels, chronic oral studies using even lower exposure levels are needed to evaluate potential adverse effects on the immune system. A single clinical study reported late-developing changes in the skin following chronic application of solid strontium (external exposure) to treat hemangioma (Bekerus 1970). It is not clear that the database needs a chronic dermal study of radiostrontium applied to the skin in a form that might be absorbed, since significant dermal absorption of strontium only occurs through abraded skin (see Section 3.5.1.3).

An increase in the incidence of leukemia has been reported in the Techa River cohort, which received doses of 10 rem (0.1 Sv) or more from radioactive strontium (Kossenko 1996; Kossenko et al. 2000). Chronic oral administration of radioactive strontium was shown to increase the incidence of bone-associated cancer in animals (Book et al. 1982; Clarke et al. 1972; Finkel et al. 1960; White et al. 1993; Zapol'skaya et al. 1974). No chronic inhalation or dermal studies were located. Since the dynamics of strontium uptake into bone are known, estimations of the risk of cancer in humans following inhalation

exposure can be derived using dose-response data from the Techa River cohort and the beagle inhalation studies. There is no realistic scenario for chronic dermal exposure at damaging levels.

Genotoxicity.

Stable Strontium. *In vitro* studies listed in Table 3-6 demonstrate a lack of adverse effects from treatment with stable strontium. A single gavage study in mice is the only evidence for genotoxicity of stable strontium (at doses of 140–1,400 mg/kg), but it seems likely that the bolus delivery may have influenced the outcome (Ghosh et al. 1990). None of the intermediate-duration studies (no chronic study is available) presented any evidence of effects that could be attributed to genotoxicity. Additional genotoxicity studies on stable strontium appear to be unnecessary.

Radioactive Strontium. The genotoxicity of radioactive strontium is well-documented. In the Techa River cohort, an elevated frequency of stable chromosomal translocations was observed (Bauchinger et al. 1998). Other evidence includes *in vitro* cytogenetic studies (see Table 3–6), and, by implication, the increased cancer rates that were observed in most investigations (see Data Needs for Cancer). However, the mechanism of radiostrontium genotoxicity (i.e., the specific DNA alterations that occur following exposure) has yet to be characterized. Recently, Sutherland et al. (2000a, 2000b) developed molecular biological assays for characterizing clustered DNA lesions caused by exposure to gamma radiation. If such a technique were to be developed for radiostrontium-exposed cells, it might provide a means of recording molecular damage.

Reproductive Toxicity.

Stable Strontium. There is no evidence regarding the effect of stable strontium on reproduction, but levels of exposure possible by inhalation or dermal routes are not likely to be harmful. Stable strontium was found to have beneficial effects when it was used in solutions designed for testing the functional capacity of human spermatozoa *in vitro* (Mortimer 1986; Mortimer et al. 1986). The possible consequences of excess strontium ingestion on reproduction need to be explored. Such experiments should compare the relative toxicity of stable strontium compounds that have different properties and may have different rates of absorption (e.g., strontium chloride, strontium carbonate and strontium phosphate).

Radioactive Strontium. In the Techa River cohort, average radiation doses to the gonads of up to 74 rem (0.74 Sv) had no effect on birth rate, fertility, or the incidence of spontaneous abortions (Kossenko et al. 1994). However, the contribution of radiostrontium to the gonadal radiation dose is likely to have been

negligible compared to that of external gamma radiation. Multigenerational oral studies in animals demonstrated a dose-dependent effect of radioactive strontium on reproduction. In pigs, only the highest doses affected fetal survival, and in those treated as adults, there was no effect on litter size, percentage of stillborn, or birth weight (Clarke et al. 1970, 1972; McClellan et al. 1963). Injection studies have reported a higher incidence of adverse reproductive effects, perhaps because of the higher dose levels. Injection of male mice prior to mating increase the rate of fetal death, and there is some evidence that radioactive strontium selectively accumulates in the testis (Reddi 1971). Injection of pregnant female mice reduced the reproductive capacity of female offspring, reducing the numbers of oocytes of all stages in the ovary (Rönnbäck 1981a, 1981b). Thus, the fetal reproductive system appears to be vulnerable to radioactive strontium. Further studies to evaluate the dose-response of gonadal effects, including cytogenetic aspects, would appear to be warranted.

Developmental Toxicity.

Stable Strontium. The main developmental effect of stable strontium is impaired bone development (rickets) following oral exposure at high doses (Johnson et al. 1968; Kshirsagar 1976; Marie and Hott 1986; Neufeld and Boskey 1994; Ögzur et al. 1996; Reinholt et al. 1984; Storey et al. 1961, 1962). Inhalation and dermal exposures are unlikely to be high enough to have an adverse effect. The oral developmental toxicity studies have concentrated on the initiation of rickets in young children or young animals during the postnatal or juvenile periods, but none have addressed the effect of maternal exposures on the fetus during gestation or on the neonate during lactation. The relative effectiveness of strontium compounds that have different properties (e.g., strontium chloride, strontium carbonate, and strontium phosphate) needs to be evaluated with regard to maternal absorption, placental transfer, fetal toxicity, and postnatal toxicity during lactation. In addition, behavioral testing should be conducted on the young animals to determine whether there are any neurological consequences of fetal exposure to excess stable strontium.

Radioactive Strontium. In the Techa River cohort, individuals who were exposed to high levels of radiostrontium as teenagers had a higher frequency of stable transformations than those who were adults at the time (Bauchinger et al. 1998); the differences were attributed to increased skeletal incorporation of radiostrontium in the young. The progeny of the exposed cohort showed an elevated incidence of adverse pregnancy outcomes (mortality from developmental anomalies, chromosomal anomalies, labor complications, and other unspecified perinatal conditions), but no increase in the incidence of cancer (Kossenko et al. 1994). Multigenerational oral studies in animals showed no teratogenic effect of radioactive strontium administered from the time of conception, but showed reduced survival of the F1

generation because of an increased incidence of bone-associated cancer (Clarke et al. 1970; Finkel et al. 1960; McClellan et al. 1963). Injection of high doses of radioactive strontium during gestation had teratogenic effects on the fetus, primarily skeletal abnormalities (Hopkins et al. 1967; Finkel and Biskis 1969). Injections had qualitatively different effects depending on the day of gestation, because of regional differences in rates of bone mineralization during gestation. More information is needed regarding the effect of the timing of maternal exposure relative to developmental stages. In addition, developmental studies that evaluate neurological effects in the offspring are needed.

Immunotoxicity.

Stable Strontium. There is no evidence that oral or dermal exposures to stable strontium affect the immune system. However, one case report described an anaphylactic reaction to inhalation of smoke that contained ~30% strontium among other irritants (Federman and Sachter 1997). Strontium's possible involvement is supported by reports that excess strontium elicits degranulation of mast cells *in vitro*, causing histamine release (Alm and Bloom 1981a, 1981b; Atkinson et al. 1979; Foreman 1977; Foreman and Mongar 1972a, 1972b; Foreman et al. 1977). For this reason, a short-term inhalation study would help to determine whether strontium by itself can elicit anaphylaxis and, if so, identify the effective concentration levels.

Radioactive Strontium. There is evidence that immunosuppression, resulting from irradiation of bone marrow, may occur in humans and animals following absorption of radioactive strontium. Immunological effects were noted in the Techa River cohort, which received relatively high radiation doses to bone marrow following ingestion of food and water contaminated with radiostrontium (Akleyev et al. 1995). In animal studies, the lowest applied inhalation or oral doses were reported to result in lymphopenia lasting as long as 2 years (Benjamin et al. 1976c; Howard 1970; Jones et al. 1976). There appears to be a need for studies that examine the effect of a lower range of exposures on immune function. Another reason for such studies comes from the reports demonstrating that NK cells may be preferentially eliminated following injection of ^{89}Sr or ^{90}Sr (Emmanuel et al. 1981; Gidlund et al. 1990; Haller and Wigzell 1977; Wiltrout et al. 1989), with the result that the organism's ability to defend against lymphoid tumors is impaired (Haller and Wigzell 1977; Luevano et al. 1981). The implication is that reduced cellular defenses may compound the effect of genotoxicity, increasing the risk of cancer. However, it is not known whether NK cells are equally vulnerable at lower exposure levels.

Neurotoxicity.

Stable Strontium. The only evidence for neurotoxicity of stable strontium is a report of hindlimb paralysis following intermediate-duration ingestion of excess strontium (Johnson et al. 1968). Given the absence of any other evidence for neurotoxicity, it is possible that, in this case, the paralysis may have resulted from compression of the hypertrophic epiphyseal cartilage, which was insufficiently mineralized to support the weight of the body. Additional neurotoxicity studies in adult animals for stable strontium do not appear to be necessary.

Radioactive Strontium. Neurological effects were reported in the Techa River population that was exposed to radiostrontium from water and food contaminated from releases at a plutonium processing plant between 1949 and 1956 (Akleyev et al. 1995). However, external gamma radiation, also released at this time, undoubtedly contributed to these effects. A single instance of epilepsy in a dog exposed by inhalation to a high concentration represents the only evidence for neurotoxicity of radioactive strontium in animals (Gillett et al. 1987b). The authors concluded that epilepsy was not related to treatment. However, no studies have specifically measured behavioral or neurological deficits in exposed animals. The database needs studies that measure neurological effects in offspring following exposure *in utero* and/or during lactation.

Epidemiological and Human Dosimetry Studies.

Stable Strontium. Strontium is ubiquitous in the environment, so everyone is exposed to it to some degree. Children who exhibit pica behavior or persons living in areas with high levels of strontium in the drinking water may have higher exposures than the general population. A Turkish epidemiological study demonstrated a higher incidence of rickets among children living in rural communities whose diet was based on grain crops grown in local soil containing high levels of strontium (Özgür et al. 1996). This study did not attempt to measure strontium levels in the affected children. In addition, this study may not be directly applicable to conditions in the United States, given the different diet and the availability of foods from a wider geographic range. One epidemiological study found that relatively high levels of strontium in the drinking water had no adverse effect on cardiovascular health, and, in fact appeared to have a beneficial effect on the rate of mortality from hypertension with heart disease (Dawson et al. 1978). Information regarding the higher levels in drinking water could be used to design animal experiments for evaluating chronic exposure effects, which are currently lacking in the database. In one case-control study that tried to account for the higher incidence of liver cancer in 1984 on Chongming

Island in China, no association was found with the levels of stable strontium detected in hair (Wang et al. 1990).

Radioactive Strontium. Dosimetry data are available for approximately 16,000 members of the Techa River population that was exposed to radiostrontium because of releases from a plutonium processing plant between 1949 and 1956 (Kossenko et al. 1997). Since exposure levels in this population were 30–100 times higher than the maximum exposure from global fallout, this cohort represents the largest group of subjects available for examining health effects of chronic radiation exposure. Subpopulations living in certain regions within the Techa River area received different levels of exposure, so that dose relationships are being established for health effects. In addition, investigators have been able to examine the effect of developmental age at the time of exposure on health outcomes. Although individuals were exposed to multiple sources of radiation during the first years (including ^{137}Cs bound in soft tissues), in recent decades, their radiation exposure was primarily from ^{90}Sr incorporated into bone. The health effects have been similar to those observed for animals exposed chronically to radiostrontium, and have included suppression of hematopoeisis and leukemia (Akleyev et al. 1995; Kossenko 1996; Kossenko et al. 1997, 2000).

A Danish epidemiological study found no association between the incidence of thyroid cancer in Denmark between 1943 and 1988 and the levels of skeletal incorporation of ^{90}Sr from fallout (Sala and Olsen 1993). However, the reason for this study is uncertain since strontium is not taken up preferentially in the thyroid, unlike iodine, which is incorporated into thyroid hormones (T_3 and T_4). A Scottish epidemiological study found no evidence for increased risks of total cancers, leukemia and non-Hodgkin's lymphoma, or acute myeloid leukemia for cohorts of children born during the period of highest fallout (radiostrontium) exposure (Hole et al. 1993). The few cases of bone tumors showed a nonsignificant increase for children born during the 'high risk' period. The reduction in fallout from above-ground nuclear weapons testing has reduced the exposure of the general population to radioactive strontium. Currently, populations working at or living in the vicinity of nuclear power plants or reprocessing facilities might have higher than background exposures. Workers at the facilities may have less exposure because protective equipment and safety procedures are in use. Environmental levels of radiostrontium that are measured near these facilities could be used to guide exposure levels in the toxicity experiments proposed above.

Biomarkers of Exposure and Effect.

Exposure.

Stable Strontium. Levels of stable strontium can be measured in blood or urine to determine exposures of any duration. Within a few days, most of the retained strontium is found in bone, but because of bone remodeling, strontium will be released over time and be detectable in blood and urine. Inductively coupled plasma mass spectroscopy (ICP-MS) was able to detect strontium in amniotic fluid and maternal plasma at levels of 0.03 and 0.06 ppb, respectively, in untreated humans (Silberstein et al. 2001). The sensitivity of this method is adequate to detect unusual accumulations of strontium. No additional biomarkers of exposure to stable strontium appear to be needed.

Radioactive Strontium. Exposures to radioactive strontium can be determined readily by measuring levels of radioactivity in blood or urine by liquid scintillation counting techniques. In addition, whole body counters can determine the level of radiostrontium retained in the skeleton. There appears to be no need for additional biomarkers of exposure to radioactive strontium.

Effect.

Stable Strontium. The typical signs of rickets (craniotabes, rachitic rosary, bulging at the wrist, genu valgus, genu varus, and delayed closure of the fontanelles) represent biomarkers of exposure to excess stable strontium in children (Özgür et al. 1996). Excess strontium ingestion has been shown to depress serum levels of 1,25-dihydroxyvitamin D in rats (Armbrecht et al. 1998). Since vitamin D insufficiency by itself can also cause rickets, measurement of both vitamin D levels and strontium levels in serum would be required to determine the role of strontium in a particular case. As mentioned above (Data Needs for Acute-Duration Studies), the proposed toxicity studies could be used to develop biomarkers for early effects following exposure to excess strontium. An array of biomarkers could possibly be developed to monitor the course of pathology before the signs of rickets fully appear.

Radioactive Strontium. A reduction in blood cell counts is a biomarker of effect for radioactive strontium. However, many other conditions can have the same result. Cytogenetic analysis of blood cells can reveal whether exposure to radioactive strontium has been sufficient to cause genotoxicity (see Table 3-5). A new method for evaluating DNA damage in cells exposed to gamma radiation has been developed using molecular biological techniques (Sutherland et al. 2000a, 2000b). It may be possible to

develop such an assay for evaluating exposure to radioactive strontium, which would also specifically identify the kind of DNA lesions produced.

Absorption, Distribution, Metabolism, and Excretion. More information is needed comparing the relative rates of absorption for different chemical forms of strontium that may vary in solubility. Solubility differences would affect the duration of residence of particles in the lung, which might have significant effects in the case of radiostrontium exposure. A comparison of gastrointestinal absorption rates for different chemical forms and for different vehicles of administration (food or water) has not been conducted. Results of such studies would help predict outcomes following different kinds of exposure. Nothing is known regarding dermal absorption of strontium taken up in soil, which is a type of exposure that children would be likely to encounter. However, studies of dermal absorption from soil would be of low priority given that significant dermal absorption of soluble strontium only occurred through abraded skin (See Section 3.5.1.3) and the amounts available from dry soil would be biologically insignificant under any realistic exposure scenario. Absorbed strontium is understood to distribute primarily to the bone and to be retained longer in the young than in adults. The combination of the ICRP PBPK model for strontium and animal-based studies on Observed Ratios of strontium and calcium (Comar and Wasserman 1964) is sufficient to estimate strontium turnover during pregnancy and lactation and in the elderly.

Comparative Toxicokinetics. The target organ for stable and radioactive strontium is the same in humans and animals, namely, bone. Young rats can serve as a model for children's exposures, but adult rats are less suitable, since the epiphyseal plate remains cartilaginous into adulthood (Leininger and Riley 1990). For this reason, adult rats could be expected to incorporate proportionally higher levels of strontium than adult humans. Furthermore, remodeling of bone in rats is not analogous to that in humans. The rat would probably not be a good model for evaluating placental transfer of strontium to the fetus because of differences in placental tissue organization.

Methods for Reducing Toxic Effects. Both stable and radioactive strontium are readily absorbed by the intestine, apparently through calcium transporter elements (Bianchi et al. 1999; Blumsohn et al. 1994; Milsom et al. 1987; Reid et al. 1986; Sips et al. 1994). Numerous methods have been tested for alleviating the effects of exposure to strontium (see Section 3.12). Oral administration of alginates with a high guluronic acid content or a single dose of aluminum phosphate antacid gel are currently recommended for reducing peak absorption of strontium shortly after exposure. The toxicities of excess stable and radioactive strontium are related to their rapid sequestration into bone. Most strategies for treatment involve high calcium in combination with other agents to enhance the replacement of strontium

in bone by calcium. There does not appear to be a need for new studies at this time. However, as mentioned in Section 3.6.2, polymorphisms in genetic factors that may affect rates of strontium absorption and bone mineralization are currently under investigation and potentially could regulate the effectiveness of treatment. If relevant polymorphisms are identified, then the existing methods for reducing toxic effects should be tested using stable strontium tracers to determine whether genetic factors affect the outcome of treatment.

Children's Susceptibility.

Stable Strontium. The effect of excess stable strontium ingestion on bone development is well documented: strontium-induced rickets has been reported in children and young animals. The particular vulnerability of children, because of the immaturity of the skeleton, is well understood. The intestinal rate of strontium absorption and the retention of strontium in the developing bone is known to be higher in infants and children than in adults. It is known that the fetus can be exposed to strontium following previous maternal exposure, but adequate information regarding changes in the rates of strontium mobilization from the maternal skeleton or changes in rates of intestinal absorption of strontium during the course of pregnancy is lacking. There is a need for studies to develop this information to fill in gaps in existing PBPK models for strontium; this effort would have the additional benefit of being applicable to other bone-seeking radioisotopes. Another issue to be considered is the relative bioavailability of strontium in the different chemical compounds (e.g., strontium chloride, strontium carbonate, strontium phosphate). Since children may be exposed to strontium by pica behavior, there is a need for animal studies that would investigate variations in absorption (bioavailability) when strontium is ingested in the form of soil.

Biomarkers of exposure and effect are established for children. Since the primary biomarker of effect, rickets, is a late-stage phenomenon, it would be useful to precisely establish a constellation of biomarkers that would identify a precursor condition. Such markers might include relative serum levels of vitamin D, calcium, phosphorus, and alkaline phosphatases, as well as strontium itself. The alginate method for reducing peak absorption of strontium has been validated in children (Sutton et al. 1971a).

Radioactive Strontium. Numerous oral exposures have demonstrated the enhanced risk of reproductive effects and cancer in animals exposed to radiostrontium *in utero* or during lactation. At the higher levels used in injection studies, teratogenic effects were observed on bone development. The possibility of neurological deficits from gestational exposure to radioactive strontium, resulting from radiostrontium incorporation into the cranium and subsequent irradiation of adjacent brain tissue, should be explored.

The toxicokinetic and bioavailability issues mentioned in the previous section on stable strontium apply to radioactive strontium. Low-level exposure studies should be conducted to evaluate possible impairment of immune function, which results from irradiation of bone marrow by radiostrontium incorporated into bone and which has been observed in animal studies at higher levels.

Radioactive strontium is its own biomarker of exposure in children and adults. The primary biomarkers of effect, also applicable to children and adults, are a reduction in lymphocyte and other blood cell counts, which closely match the intensity of exposure. The alginate method for reducing peak absorption, described above, has been validated for children (Sutton et al. 1971a). It is not clear whether another recommended treatment, a single dose of aluminum phosphate antacid gel, would be safe for children, since it can have toxic effects in children at high doses. Either method would only be effective if administered very soon after exposure (within an hour).

Data needs relating to both prenatal and childhood exposures and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

Stable Strontium. Two currently funded research programs that specifically mention stable strontium are probably using it as a surrogate for calcium in physiological experiments. In a study sponsored by the National Institute of Mental Health, Dr. J.A. Dzubay (1997) of the Oregon Health Sciences University is conducting *in vitro* experiments on the activity of NMDA (N-methyl D-aspartate) channels in the hippocampus; these are membrane channels controlled by NMDA receptors that regulate the influx of calcium into neurons. In work funded by the National Institute of Neurological Disorders and Stroke, Dr. David Lovinger (1999) of Vanderbilt University Medical Center is studying glutamatergic and dopaminergic synaptic transmission in the neostriatum. In a third study, sponsored by the National Institute of General Medical Sciences, Dr. J. Bell (1998) of Fayetteville State University in North Carolina is examining the effect of metal salts on the fidelity of DNA synthesis. It appears that this research may provide additional genotoxicity information regarding stable strontium.

Radioactive Strontium. The single largest population available for studying the long-term health effects of radiostrontium is the Techa River cohort that was exposed from contaminated drinking water and food following releases from a plutonium processing plant between 1949 and 1956 (Akleyev et al. 1995; Bauchinger et al. 1998; Kossenko 1996; Kossenko et al. 1994, 1997, 2000; Shagina et al. 2000; Tolstykh et al. 1998). In addition to the studies reviewed in this toxicological profile, further analysis of this population is expected to continue under the auspices of the Urals Research Center for Radiation Medicine.

Additional information regarding the toxicity of radioactive strontium is likely to emerge from studies related to the therapeutic use of strontium isotopes. In programs funded by the National Heart Lung and Blood Institute, Dr. Sou-Tung Chiu-Tsao (1999) of the Beth-Israel Medical Center, New York, and Dr. Ravinder Nath (1999) of Yale University Medical Center, are investigating ^{90}Sr along with other isotopes for intravascular brachytherapy delivered at the time of angioplasty. Dr. Carl J. Pepine (1998) of the Department of Veterans Affairs Medical Center, Gainesville, Florida, is conducting a clinical trial to evaluate a commercial product for intravascular brachytherapy. Dr. Timothy Kuzel (1999) of the Department of Veterans Affairs Medical Center, Chicago, Illinois, is conducting a Phase I/II trial of ^{89}Sr in conjunction with mitoxantrone and hydrocortisone in the treatment of bone metastases in patients with hormone-refractory prostate cancer. In work funded by the National Center of Research Resources, Dr. Franco Muggia (1999) of the New York University Medical Center is conducting an open label Phase II study to evaluate the effect and toxicity of Doxil, a liposomal encapsulated doxirubicin, and ^{89}Sr in combination for treating hormone-refractory metastatic prostate cancer. In a study sponsored by the National Institute on Deafness and Other Communication Disorders, Dr. Gina M. Nelson (1999) of the University of Alabama at Birmingham is conducting laboratory tests in rodents in order to develop a radiation treatment for cancer of the mouth that will be less likely to destroy the sense of taste than current procedures. Radiostrontium will be held in a device to expose the tongue to beta radiation.