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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO STRONTIUM IN THE UNITED STATES

Stable Strontium. Elemental strontium (atomic number 38) occurs naturally in the earth's mantle as a mixture of four stable isotopes, ^{88}Sr, ^{86}Sr, ^{87}Sr, and ^{84}Sr, and is present everywhere in very dilute concentrations. It is very similar to calcium in its environmental and physiological behavior. Strontium is generally found in molecular compounds with other elements. Commercially important strontium minerals include celestite ($SrSO_4$) and strontianite ($SrCO_3$). Strontium is used in the manufacture of ceramics and glass products, primarily in the faceplate glass of televisions and other cathode-ray-tube devices, where it serves to block x-ray emissions.

The general population is exposed to stable strontium primarily by ingestion of food and water, and to a lesser degree, by inhalation. The strontium content in air averages 20 ng/m^3, with higher concentrations resulting from stack emissions from coal-burning plants. Strontium is present in nearly all fresh waters in amounts generally ranging between 0.5 and 1.5 mg/L, with higher levels occurring where there are celestite-rich limestone deposits. The average concentration of stable strontium in soil is approximately 240 mg Sr/kg, but agricultural soils may be treated with phosphate fertilizer or limestone, which contain ~610 mg Sr/kg. Because strontium is chemically similar to calcium, it is taken up from the soil by fruits and vegetables. The average concentration of strontium in fruit produce ranged from 0.0416 to 2.232 µg/L. The total estimated daily exposure to stable strontium is approximately 3.3 mg/day (0.046 mg/kg/day): 400 ng/day from inhalation, 2 mg/day from drinking water, and 1.3 mg/day from the diet (see Chapter 6). Assuming a reference body weight of 70 kg, the typical daily strontium exposure is 46 µg/kg body weight. The strontium content of the human body is approximately 4.6 ppm by weight, 99% of which is localized in bones and teeth. Blood concentrations of strontium are in the range of 20–31 µg/L.

Radioactive Strontium. The radioactive isotopes of strontium do not occur naturally but are produced as a by-product of nuclear fission of ^{235}U, ^{238}U, or ^{239}Pu. The most significant isotopes are ^{90}Sr (half-life of 29 years), ^{89}Sr (half-life of 51 days), and ^{85}Sr (half-life of 65 days), which decay by the emission of beta particles. ^{90}Sr is currently found in spent fuel rods in nuclear reactors and is considered a waste product. Other radioactive strontium isotopes have been employed for medical uses: ^{89}Sr (as Metastron™) as a cancer therapeutic for the relief of bone pain and ^{85}Sr in the radiologic imaging of bone. ^{85}Sr also has

minor commercial applications in thermoelectric power generation, as a beta particle standard source, and in instruments that measure the thickness and density of materials. Disposal and handling of radioactive strontium isotopes are regulated by the U.S. Nuclear Regulatory Commission.

The general population is exposed to very small amounts of radioactive strontium from the ingestion of contaminated water and food; inhalation exposure is negligible. The average concentration of ^{90}Sr in drinking water in 1994 was estimated as 0.1 pCi/L; after 1994, estimates were based on gross beta activity and not reported by individual elements since the amounts were so small. Fresh vegetables contribute more than one third of the yearly dietary intake of ^{90}Sr, followed by grains and dairy products. The current total daily exposure levels to radioactive strontium are estimated to be approximately 5.2 pCi/day (0.16 Bq/day; 0.074 pCi/kg/day): 5 pCi/day from food and 0.2 pCi/day from drinking water.

See Chapter 6 for more detailed information regarding concentrations of stable and radioactive strontium in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Stable Strontium. There is no direct evidence that stable strontium is toxic to humans under normal environmental exposures. The primary toxicological effect of absorbed excess strontium in laboratory animals is abnormal skeletal development (rickets), which occurs only at relatively high oral doses. The inhalation toxicity of pure stable strontium has not been evaluated. At levels normally encountered in the environment, strontium appears to have low toxicity to adults or to juveniles with adequate nutrition. Juveniles, especially those with poor nutrition, are vulnerable because strontium, as an imperfect surrogate for calcium, interferes with bone mineralization in the developing skeleton. The data for adverse health effects of stable strontium in humans are sparse, but indicate a possibility of skeletal effects under special circumstances: an epidemiological study of strontium-related rickets in Turkish children and a few studies of hemodialysis patients who developed osteomalacia because of strontium in dialysis water. Numerous animal studies demonstrated adverse effects on skeletal development in juveniles following ingestion of excess stable strontium (discussed below under Skeletal Effects). No developmental or reproductive studies have been conducted involving exposure to stable strontium during gestation. No studies examined whether stable strontium is carcinogenic to humans or animals. One strontium compound, strontium chromate, is a genotoxic human carcinogen by the inhalation route, but the hazard is caused by hexavalent chromium and not strontium.

Other effects have been observed sporadically and are of unclear physiological significance. Paralysis of the hindlimbs was observed in orally-exposed rats, but it is uncertain whether the cause was neurophysiological or the result of local neuronal damage secondary to deformation of the femora. Minor unspecified changes in hepatic histology and glycogen content were observed in orally-exposed rats. The following section discusses effects in the primary target of stable strontium, the skeleton, in greater detail.

Skeletal Effects. Although strontium, as a molecular surrogate for calcium, can be distributed throughout the body, its main target for deposition is the skeleton. One suggestive epidemiological study found that increased strontium ingestion contributed to an increase in the prevalence of signs of rickets (craniomalacia, rachitic rosary, bulging at the wrist, bony deformities of the leg, and delayed closure of the fontanelles) in children in a region of Turkey. A significantly increased incidence of rickets was associated with a diet restricted to water and cereals grown locally in soils with strontium concentrations in excess of 350 mg/kg. Other contributing factors included probable deficiencies in vitamin D, protein, and calcium after weaning; breast feeding for >2 years appeared to be a protective factor against the development of rickets in this population. The only reports of strontium-related skeletal problems in adults concerned osteomalacia in hemodialysis patients exposed to strontium in dialysis water. Dialysis patients may be unusually susceptible because of their impaired handling of strontium. Stable strontium compounds have been used for the treatment of osteoporosis (see Section 2.3).

Animal studies strongly support the identification of bone as the most sensitive target of strontium toxicity. Relatively high doses of strontium (≥500 mg/kg/day) caused a reduction in bone mineralization (ash weight) and an alteration in the chemical composition of organic bone matrix. In addition, the hypertrophic zones of the epiphyseal growth plates of long bones became abnormally deep and wide, as calcification failed to occur. Severe weakening of the bones resulted from rickets, in which the skeleton could not support the body adequately; deformity of the head of the femur may have contributed to paralysis of the hind limbs in some cases. Young animals were more sensitive to the effect of excess strontium than older animals, possibly because the absorption and retention of strontium were higher in the young. In addition, inadequate calcium and vitamin D in the diet increased the severity of skeletal effects. The chemical form of strontium may influence toxicity by affecting gastrointestinal absorption. One intermediate oral animal study that tested strontium phosphate reported a much higher no-effect level than studies that tested strontium chloride or carbonate. However, cation effects on strontium toxicity have not been studied systematically.

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Evidence from the few human studies and numerous animal toxicity studies suggest that healthy adults living near hazardous waste sites are unlikely to be exposed to levels of stable strontium sufficiently high to cause adverse skeletal effects. Children living in areas where the soil and drinking water contain relatively high amounts of strontium may be vulnerable to skeletal effects if their nutritional status is poor (deficient in calcium, vitamin D, and/or protein) and if the diet is restricted to foods grown locally. All these conditions are not likely to be common in the United States, since the food supply generally comes from a wide geographic area.

Radioactive Strontium. Exposure to radioactive strontium can result in health consequences that vary depending on the dose, the route of exposure, and the chemical form. Both ^{90}Sr and ^{89}Sr emit beta particles, which, in tissue, may ionize cellular molecules within a range of 1 cm, resulting in tissue damage and disruption of cellular function if the capacity of natural repair mechanisms is exceeded. Adverse health effects occur at high levels of exposure that significantly exceed background levels encountered by the general population. It should be noted that no discernable adverse health effects were detected in the general population from chronic low-level exposure to ^{90}Sr in fallout during the period of aboveground weapons testing.

^{90}Sr represents the most significant isotope of concern because of its relatively long half-life (29 years) and because of the bone-seeking properties of strontium. The most serious effects of oral exposure to absorbed radioactive strontium are necrotic lesions and cancers of bone and the adjacent tissues. High level acute exposures can destroy hematopoietic bone marrow, leading to acute radiation syndrome (see below), the primary cause of mortality in the short term. At lower doses, irradiation of bone marrow may lead to chronic suppression of immune function.

The consequences of inhalation exposures in animals vary depending on the solubility of the form of radiostrontium. Insoluble particles tend to be retained in the lung, resulting in pneumonitis; necrosis of the pulmonary, vascular, and adjacent myocardial tissues; pulmonary fibrosis; and, later, pulmonary and vascular cancers. Inhalation of soluble radiostrontium does not have these local effects because the material is absorbed and distributed in the skeleton. The effects of inhalation of soluble strontium are, therefore, similar to those described for the oral route: acute radiation syndrome and other hematopoietic effects, osteosarcoma, and immunosuppression.

External exposure to solid strontium sources placed near the skin or eye can cause local lesions when doses are significantly higher than background. Effects observed in clinical studies on the eye included

keratitis or scarring of the cornea, telangiectasis or scarring of the conjunctiva, iritis, conjunctivitis, mild irritation, and scleral thinning. Dermal effects in clinical studies range from erythema and pigmentation changes, dry and moist desquamation (which involves destruction of the basal epithelial cells), and telangiectasis and increased vascular permeability, to long-term responses such as epithelial and dermal hyperplasia, chronic fibrosis, and dermal atrophy.

There is inconclusive evidence in humans and definitive evidence in laboratory animals that exposure to radioactive strontium at very high doses *in utero* can lead to adverse developmental effects. Slight increases in developmental effects were noted in a population of the former Soviet Union whose drinking water (the Techa River) was contaminated with multiple radioactive elements released from a plutonium production plant between 1949 and 1956. These effects included 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 exposed individuals. However, the specific contribution of radiostrontium to these effects is not known. Developmental effects in laboratory animals were noted at extremely high doses, as if, on a kilogram body weight basis, individual pregnant females were receiving daily the entire amount of ^{90}Sr currently released from one nuclear power plant into the environment during a year (see Table 6-1). There is evidence that maternal oral exposure to radioactive strontium can lead to reduced fetal and postnatal survival in the offspring, but there is no evidence for birth defects. At the very highest doses of radioactive strontium injected into pregnant females, the offpsring exhibit increases in birth defects (skeletal anomalies and partial atelectasis of the lungs), and cancers of soft tissues near bone (meningeal and pituitary tumors), as well as hyperplasia of lymph nodes and spleen and deficient hematopoiesis. Exposure to radioactive strontium in milk from dams injected at very high doses reduces the numbers of early-stage oocytes in the ovary of neonatal mice, but the effect is less severe than when offspring are exposed only *in utero*.

There is no evidence in humans that radioactive strontium leads to reproductive effects, but there is some evidence in laboratory animals. Although the Techa River populations received the highest known extended oral exposure to radioactive strontium (and other radionuclides) of any human group, there were no significant effects on reproductive parameters (birth rate, fertility, incidence of spontaneous abortion). An increase in fetal deaths was noted in some studies in rats, but no reproductive effects were noted in larger laboratory animals at equivalent oral doses. This difference appears to be related to the fact that in small animals, the bone marrow cavity diameters are not wide enough to leave the central hematopoetic tissues untouched by beta-irradiation emitted by radioactive strontium bound to bone. Exposure to high

doses of radioactive strontium by injection led to significant reproductive effects (reduced fertility, reduced gonadal cellularity, suppressed spermatocyte maturation) in mice.

Other effects of radioactive strontium have been observed sporadically in animal studies and are of unclear physiological significance. Anorexia, reduced body weight, and liver effects that were possibly secondary to radiation pneumonitis (chronic passive congestion of the liver and mild centrilobular hepatic fibrosis) were observed in beagles following a single inhalation exposure of insoluble ^{90}Sr particles at an initial lung burden of 25 μCi/kg.

The populations potentially most sensitive to radiostrontium exposure include the young and individuals that have poor nutrition or deficiencies in vitamin D. Infants and children are more vulnerable than adults because they absorb strontium through the gastrointestinal tract at slightly higher rates and because they have actively growing bones that incorporate more strontium than mature bones. Very high prenatal exposure levels may cause major developmental anomalies in the skeleton and adjacent areas if critical tissues are destroyed. In addition, since children have a higher proportion of mitotic cells than adults, their rates of genotoxic damage are higher. This is because genetic lesions become fixed mutations when mitosis occurs before genetic damage is repaired. Genetic lesions in genes controlling the cell cycle can lead to the development of cancer and may be the basis of excess cancer cases attributed to exposure to radioactive strontium. Individuals with poor nutrition or deficiencies in vitamin D, such as those with osteomalacia, are theoretically more vulnerable to radioactive strontium because their lower absorption of calcium results in relatively higher rates of strontium incorporation into bone during the remodeling process that continues throughout life. The level of incorporation of radiostrontium into bone can be somewhat reduced by ingestion of alginates soon after exposure. Removal from bone after incorporation is not feasible.

The major adverse effects of exposure to radioactive strontium, non-cancerous lesions of hematopoietic bone marrow tissue, cancer, and dystrophic lesions of the skeleton, are discussed below in greater detail. It should be noted that the large animal studies are more relevant than rodent studies to humans because the severity of bone marrow effects is inversely proportional to the diameter of the bone marrow cavity.

Non-Cancerous Bone Marrow Effects (Including Acute Radiation Syndrome). Bone marrow effects are the most serious immediate consequences of exposure to high levels of radioactive strontium by either the inhalation or oral route. When absorbed radioactive strontium incorporates into bone, irradiation of the bone marrow results in hypoplasia of the hemopoietic tissue and pancytopenia,

with the severity depending on the dose. At the highest doses, acute radiation syndrome (anorexia, bloody diarrhea) would be expected because of the virtual destruction of the bone marrow. Acute radiation syndrome was not observed in the orally-exposed Techa River population, but was observed in dogs several weeks after receiving long-term retained body burdens of ≥47 μCi ^{90}Sr/kg (≥1.74 MBq/kg) following a single exposure to soluble $^{90}SrCl_2$ by inhalation. Hemorrhaging is caused by the drastic depression in platelet counts; a severe drop in neutrophil counts precedes death. At lower exposure levels, pancytopenia is detectable, but is not immediately life-threatening. This was observed in dogs that received long-term retained burdens >10 μCi ^{90}Sr/kg (>0.37 MBq/kg) following a single inhalation exposure of soluble $^{90}SrCl_2$

At lower levels of exposure, not all types of hematopoietic cells within bone marrow are affected, possibly because of differences in intrinsic rates of replacement. In the orally-exposed Techa River populations, milder chronic effects of bone marrow irradiation were reported in a small percentage of exposed individuals: leukopenia, thrombocytopenia, and granulocytopenia, as well as lymphopenia involving T lymphocytes and large granulocytic lymphocytes. Reduced lymphocyte counts, indicators of weakened immune function, in some individuals who received radiation to the bone marrow in excess of 30 rem (0.3 Sv) per year, were implicated as the cause of the higher incidences of infectious disease in those who developed radiation-induced cancers. Suppression of the immune system is also supported by studies in pigs exposed to 625 μCi ^{90}Sr/day (23.13 MBq/day) in feed for 4–9 months or in dogs receiving single inhalation exposures of soluble (long-term retained burden >10 μCi ^{90}Sr/kg [>370 kBq/kg]) or insoluble (initial lung burden ≥5 μCi ^{90}Sr/kg [≥185 kBq/kg]) radioactive strontium. Injection studies in mice indicate that natural killer cells were preferentially eliminated. Chronic myeloid metaplasia, possibly related to genotoxicity, was another effect of bone marrow irradiation in orally-exposed pigs that received cumulative doses in excess of 40 rad (0.4 Gy) and in a small percentage of dogs that received ≥0.4 μCi ^{90}Sr/kg/day (44.4 kBq/kg/day) from mid-gestation to 1.5 years.

Cancer. Radioactive strontium, like other radionuclides, is a genotoxic carcinogen. Mutations in genes controlling the cell cycle can lead to cancer if the damage is not repaired before the next cell division; rapidly dividing cells, such as the hematopoietic cells in bone marrow, are especially vulnerable. Incorporation of radioactive strontium into bone places bone and the adjacent soft tissues at risk for cancer. Chronic consumption of radioactive strontium (and other radionuclides), leading to estimated doses to bone marrow in excess of 10 rem (0.1 Sv), significantly increased the incidence of leukemia in the Techa River population, but this effect was not observed in offspring exposed *in utero* who received lower doses. Leukemia has also been observed in animals exposed orally or by inhalation to soluble

radioactive strontium. Other cancers observed in animal studies include osteosarcomas, hemangiosarcomas, cancers of other soft tissues near bone, and, in feeding studies, nasal, oral, and periodontal carcinomas. In dogs that inhaled insoluble ^{90}Sr, the particles lodged in the respiratory tract, causing cancers of the immediately surrounding tissues: hemangiosarcomas of the lung and heart and carcinomas of the respiratory tract. External exposure to ^{90}Sr (solid source) in mice induced skin cancers (squamous cell carcinoma, basal cell carcinoma, fibrosarcoma) and, in one study, osteosarcomas. Immature organisms are potentially more vulnerable than adults to radioactive strontium partly because they have a higher proportion of cells in mitotic phase and partly because they incorporate relatively more radiostrontium into bone. In a multigenerational swine study, doses that were not carcinogenic in the females exposed as adults induced osteosarcomas in the F1 or F2 generations exposed from conception. National Council on Radiation Protection and Measurements concluded that uncertainties remain regarding extrapolation from the high doses of ^{90}Sr known to cause cancer in animals to the lower doses that might increase the incidence of leukemia in humans. The Council suggested that more basic knowledge on the mechanism of cancer induction by ionizing radiation would be required to understand the risk of internal exposure to ^{90}Sr. EPA has determined that radioactive strontium is a known human carcinogen (Group A). EPA estimated that the risk of developing cancer following exposure to 8 pCi/L in drinking water is 1 in 100,000. The International Agency for Research on Cancer has determined that internally deposited radionuclides, such as radioactive strontium, are carcinogenic to humans (Group 1).

Skeletal Effects. Dystrophic lesions of the skeleton occur when the level of oral exposure of soluble radioactive strontium is high enough that the amount incorporated into bone results in irradiation of the bone at levels exceeding natural repair mechanisms. The effect could occur by acute exposure to a very high dose, by intermediate-duration exposure at a moderate dose, or by chronic-duration exposure at a lower dose. Such lesions, primarily affecting articular and periarticular tissues, were reported in the Techa River populations that received mean radiation doses to the surface of bone in excess of 200 rem (2 Sv) following chronic oral exposure to radiostrontium, but not at the lower doses.

Animal oral exposure studies support the findings in humans. Skeletal or dental effects in adults are less severe than in developing animals because in adults, incorporation of radioactive strontium is mainly restricted to the surfaces of bone or teeth. Incorporation throughout the developing bone renders it vulnerable to weakening as a result of focal necrosis from long-term irradiation. Intermediate-exposure at 6 μCi/kg/day for 1–10 months reduced numbers of osteocytes and damaged blood vessels in the bone of adult rabbits. More severe effects damaging the bone structure (necrosis of vasculature, impaired transformation into cortical bone, and fracturing) were observed in dogs exposed *in utero* and chronically

into adulthood at 0.4 μCi/kg/day. Damage to developing teeth (disordered tooth structure and increased cell death of differentiating odontoblasts and pulp cells) has been reported in rabbits following injection of a very high dose (600 μCi ^{90}Sr/kg), but effects were less severe in mature teeth.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Stable Strontium. Data on the toxicity of inhaled stable strontium are not suitable for derivation of an inhalation MRL: one case report of a woman exposed to an undetermined concentration of strontium mixed with other chemicals in smoke from an ignited flare (Federman and Sachter 1997).

Radioactive Strontium. The main sources on the toxicity of inhaled radioactive strontium are two acute-duration studies in dogs reporting severe hematological and immunological effects following a single nose-only exposure to ^{90}Sr as fused clay particles for several minutes (Jones et al. 1976) or strontium chloride (Gillett et al. 1987a). Inhalation of ^{90}Sr fused-clay particles leading to initial lung burdens of 5 μCi ^{90}Sr/kg (185 kBq/kg) resulted in chronic significant depression of lymphocyte counts and suppression of immune function (Jones et al. 1976). Chronic thrombocytopenia and neutropenia, which persisted for 1,000 days in dogs at all tested exposure levels (long-term retained burdens at or above 1 μCi ^{90}Sr/kg; 0.04 MBq/kg), was observed in dogs exposed to soluble $^{90}SrCl_2$ (Gillett et al. 1987a). These data were not considered adequate for derivation of an acute-duration inhalation MRL because the observed hematological and immunological effects were considered severe adverse effects.

Oral MRLs

Stable Strontium.

- An MRL of 2.0 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to stable strontium and its compounds.

The most consistent effects of oral exposure to excess stable strontium are rickets (impaired cartilage calcification) and osteomalacia (impaired bone mineralization), especially in the young. One Turkish epidemiological study provided indirect evidence that excess oral exposure to strontium (in the presence of other predisposing factors) may contribute to the development of rickets in children (Ögzür et al. 1996). Overall, animal studies on strontium have concentrated on the evaluation of skeletal effects, with

occasional consideration to body weight and serum chemistry. In young rodents, typical effects of excess strontium included an abnormal widening of the cartilaginous epiphyseal plates of the long bones, a lack of bone calcification, and abnormal deposition of unmineralized bone matrix or osteoid (Johnson et al. 1968; Kshirsagar 1976; Marie and Hott 1986; Morohashi et al. 1994; Neufeld and Boskey 1994; Storey 1962). The skeletal effects of strontium are known to be related to its chemical similarity to calcium and its suppression of vitamin D metabolism and intestinal calcium absorption (Armbrecht et al. 1998). Effects are more severe in young rats than in adults because the rate of skeletal incorporation of strontium is higher in young animals (see Section 3.5.2.2).

A lowest-observed-adverse-effect level (LOAEL) of 550 mg strontium/kg/day is identified for bone mineralization abnormalities in weanling rats that were exposed to dietary strontium carbonate for 20 days (Storey 1961). The epiphyseal plates of long bones were irregular and abnormally thick. Furthermore, areas of uncalcified bone matrix were deposited in the distal ends of the metaphyseal trabeculae and proximal end of the diaphyses. Irregularities in the organization of the cells of the hypertrophic zone, in the pattern of calcification, and in the deposition of osteoid were more conspicuous with increasing dose. In tibias, the dry weight, ash weight, ash percentage, and calcium in ash were significantly reduced with increased strontium intake. No effects on bone mineralization occurred in weanling rats ingesting 140 mg strontium/kg/day, the NOAEL for intemediate-duration exposure. In adult rats examined in this study, the effects of strontium ingestion were less severe in that higher doses were required to produce the same effect. The no-effect level in adults was 690 mg strontium/kg/day, which was higher than the LOAEL for weanlings. In adults, changes in tibial histology, such as abnormal thickening of the epiphyseal cartilages and abnormally widened metaphyseal osteoid seams, were noted at or above 1,370 mg strontium/kg/day. At 2,750 mg strontium/kg/day, osteoid tissue was deposited near vascular canals and the areas of bone resorption were reduced. In adult rat tibias, the dry weight, ash weight, ash percentage, and calcium in ash were only significantly affected at the highest dose. This study demonstrates the difference in sensitivity to strontium between young and old animals, which is caused by the higher rate of strontium incorporation into the developing skeleton in young animals.

The critical dose levels identified in the Storey (1961) study are supported by other studies in rodents. Similar LOAELs (500–565 mg strontium/kg/day) for abnormal bone mineralization are identified in several studies on weanling rats exposed to strontium carbonate (Morohashi et al. 1994; Neufeld and Boskey 1994) or an unspecified form of strontium (Johnson et al. 1968). Slight skeletal effects were noted in mice exposed to 350 mg strontium/kg/day as strontium chloride (Marie and Hott 1986). In addition, similar no-observed-adverse-effect levels (NOAELs) in the range of 110–168 mg

strontium/kg/day for skeletal effects were identified from studies in weanling rats exposed to an unspecified form of strontium (Grynpas et al. 1996), strontium chloride hexahydrate (Kroes et al. 1977), or strontium carbonate (Morohashi et al. 1994). The study by Storey (1961) is preferred as the basis for the intermediate MRL because both young and adult animals were tested, the administered doses included NOAELs and LOAELs for both age groups, and the evaluation of skeletal effects included histopathological analysis. Some of the other studies have serious deficiencies that render them unsuitable for deriving an MRL. Two studies administered single doses of 166–168 mg/kg, but reported no adverse effects (Grynpas et al. 1996; Kroes et al. 1977); although the results support the NOAEL by Storey (1961), the lack of higher doses causing positive results raises uncertainty about the experiments. The study by Johnson et al. (1968) administered a single dose of 565 mg/kg that was a serious LOAEL for increased mortality. Three of the other studies had deficiencies that rendered them less suitable than Storey (1961). The study by Morohashi et al. (1994) did not analyze bone histopathology. Studies by Marie and Hott (1986) and Neufield and Boskey (1994) administered single doses of 350 and 500 mg/kg, respectively, which were LOAELs for skeletal effects, but the studies provided no information on no-effect levels or effects at higher doses. Therefore, the NOAEL of 140 mg strontium/kg/day for skeletal effects in weanling rats (Storey 1961) would appear to be the most appropriate basis for calculating an intermediate MRL. The NOAEL of 140 mg strontium/kg/day was divided by an uncertainty factor of 30 (10 for extrapolation from animal to human and 3 for human variability) and a modifying factor of 3 (for short study duration and limited end point examination). A partial uncertainty factor was used to account for human variability because the selected NOAEL was based on the response of juveniles, which is also the most sensitive human group. The resulting MRL is calculated to be 2.0 mg strontium/kg/day, which is approximately 40 times higher than the total estimated daily exposure to stable strontium of 0.047 mg/kg/day. The MRL represents an estimate of daily human exposure that is likely to be without an appreciable risk of adverse health effects. Since the MRL is based on effects in young rats, it is considered to be protective of children, who are similar with respect to immaturity of the skeleton and high intestinal rates of strontium absorption.

MRLs were not derived for acute- or chronic-duration oral exposures to stable strontium. The relevant acute data are limited to two lethality studies in mice (Ghosh et al. 1990; Llobet et al. 1991a) and two toxicity studies in rats (Kshirsagar 1976; Kroes et al. 1977). The rat studies were not considered suitable for MRL derivation. In the Kshirsagar (1976) study, the only administered dose, 3,000 mg strontium per kg/day as strontium phosphate, resulted in severe body weight effects (62% reduction in body weight gain) and was higher than the LD_{50} values reported for mice (Ghosh et al. 1990; Llobet et al. 1991a). The Kroes et al. (1977) study did not identify an adverse effect level. Limited data on the chronic toxicity of

stable strontium are available for humans and no data are available for animals. The available data involve patients with osteoporosis or other disorders of bone mineralization who were treated for several years with low doses of strontium in the form of strontium salts: strontium lactate (Shorr and Carter 1952), strontium gluconate or strontium carbonate (Skoryna 1981a, 1984), and strontium ranelate (Meunier et al. 2002, 2004; Reginster 2002, 2003, Reginster et al. 2002). None of the studies reported adverse effects on bone or significant increases in side-effects related to treatment, but reporting was poor in some of the studies (Shorr and Carter 1952; Skoryna 1981a, 1984). These data are not suitable for MRL derivation for several reasons. All subjects in these studies were co-administered calcium and some were given vitamin D, both of which are known to interfere with strontium toxicity. In addition, all of the subjects were adults, the majority being postmenopausal women with osteoporosis. Considering that the intermediate oral MRL is based upon bone effects in juvenile rats, there is reason to suspect that a chronic oral MRL based on these data would not be protective of the most sensitive population (juveniles).

Radioactive Strontium. No MRLs were derived for oral exposure to radioactive strontium, although the database includes chronic-duration human studies and acute-, intermediate-, and chronic-duration animal studies in several species. Strontium dosimetry information is available for the populations affected by contamination of the Techa River, but these exposures included simultaneous external gamma radiation from ^{137}Cs, ^{106}Ru, and ^{95}Z and internal radiation from ^{137}Cs, in addition to ^{89}Sr and ^{90}Sr (Kossenko et al. 1994). The combined exposure studies are not suitable for the derivation of MRLs. An increase in the incidence of leukemia was reported for Techa River individuals receiving estimated bone marrow doses, attributed to radioactive strontium, in excess of 10 rem (0.1 Sv) (Kossenko 1996; Kossenko et al. 1997, 2000, 2002). Dystrophic lesions of the skeleton were observed in individuals with mean radiation doses to the surface of bone in excess of 200 rem (2 Sv) (Akleyev et al. 1995). Studies on rodents are not suitable models for establishing MRL levels for human exposure to radioactive strontium because of their relatively smaller bone diameter which places their bone marrow tissues at greater risk of radiation damage. Most of the large animal studies reported serious hematological effects at all dose levels. Immunosuppression was observed in pigs fed 625 μCi ^{90}Sr/day (23.13 MBq/day) for 4–9 months (Howard 1970; Howard and Clarke 1970). Chronic myeloid metaplasia was another effect of bone marrow irradiation in orally-exposed pigs that received cumulative doses in excess of 40 rad (0.4 Gy) and a small percentage of dogs that received ≥0.4 μCi ^{90}Sr/kg/day (44.4 kBq/kg/day) from mid-gestation to 1.5 years (Dungworth et al. 1969; Howard 1970; Howard and Clarke 1970). These serious effects are not suitable bases for determining MRL levels.