Strontium; CASRN 7440-24-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Strontium

File First On-Line 10/01/1992

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1992
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Strontium
CASRN — 7440-24-6
Last Revised — 10/01/1992

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Rachitic bone **20-Day, 9-Week, and 3-Year Oral Studies in Young and Adult Rats** **Storey, 1961; Marie et al., 1985; Skoryna, 1981**	NOAEL: 0.19% Sr (as SrCO3) (190 mg Sr/kg/day) LOAEL: 0.38% Sr (as SrCO3) (380 mg/kg/day)	300	1	6E-1 mg/kg/day

* Conversion Factors: 0.19% Sr = 1900 mg Sr/kg diet. Assuming young rats consume food equivalent to 10% of their body weight/day, the actual intake is calculated to be 190 mg Sr/kg bw/day.

I.A.2. Principal and Supporting Studies (Oral RfD)

Storey, E. 1961. Strontium "rickets": bone calcium and strontium changes. Austral. Ann. Med. 10: 213-222.

Marie, P.J., M.T. Garba, M. Hott and L. Miravet. 1985. Effect of low doses of stable Sr on bone metabolism in rats. Miner. Electrolyte Metab. 11: 5-13.

Skoryna, S.C. 1981. Effects of oral supplementation with stable strontium. Can. Med. Assoc. J. 125(7): 703-712.

Storey (1961) fed young (40-60 g) and adult (200-250 g) female rats (strain unspecified; 3/group) diets with adequate calcium (1.6%), phosphorous (0.9%) and vitamin D for 20 days. The dietary levels of strontium (as strontium carbonate) given to both adult and young rats were 0.19, 0.38, 0.75, 1.0 (young rats only), 1.5 and 3.0%. Assuming young rats consume 10% and adult rats consume 5% of their body weight in food per day, these doses correspond to 190, 380,

750, 1000, 1500 and 3000 mg/kg-day for young rats and 95, 190, 375, 750 and 1500 mg/kg-day for adult rats. Rats were examined for changes in bone mineralization and defects in cartilage. They were weighed at the onset and end of the experiment. Young rats were found to be affected more severely at lower dietary Sr levels than were adult rats. In young rats at 0.38% (380 mg/kg-day) the epiphyseal plate was irregular and slightly widened; however, at 0.75% (750 mg/kg-day) this plate was so irregular that measurements were unreliable. Changes observed with the dose of 0.38% and higher were inhibition of calcification, as evidenced by increasing width of epiphyseal cartilage, presence of uncalcified bone matrix and decreased ash weight of bone. In adults, the first obvious bone change occurred at the 1.5% dietary strontium level (750 mg/kg-day) and included slightly wider than normal epiphyseal cartilage plate and metaphyseal osteoid seams, which were irregularly increased in extent and width. At the 3% strontium level in adult animals (1500 mg/kg-day), the cartilage plate was much larger. For young rats, the dietary level of 0.19% strontium (190 mg/kg-day) was a NOAEL and 0.38% strontium (380 mg/kg-day) was a LOAEL. For adult rats, the dietary level of 0.75% strontium (375 mg/kg-day) was a NOAEL and 1.5% strontium (750 mg/kg-day) was a LOAEL.

Marie et al. (1985) administered stable strontium to weanling male Spraque-Dawley rats. The purpose of this study was to determine the effect of low doses of stable strontium on mineral homeostasis and bone histology. Rats were divided into groups (8/group) receiving 0, 0.19, 0.27, 0.34 and 0.40% of SrCl2 in distilled water for 9 weeks. The diet contained 0.5% calcium. Based on body weight and water consumption data, the authors estimated average strontium intakes of 0, 316, 425, 525 and 633 mg/kg-day. The authors concluded that an oral dose lower than 0.40% (633 mg/kg-day) did not produce adverse effects on body growth or on bone mineralization. Rats in the 0.40% (633 mg/kg-day) dose group showed signs of increased mineralization lag time; excessive osteoid thickness associated with a decline in the rate of calcification, which resulted in slow growth rate; and a decreased double- labeled osteoid surface, which frequently resulted in defective long bone growth. This study identified a NOAEL of 525 mg/kg and a LOAEL of 633 mg/kg-day.

Skoryna (1981) investigated the oral toxicity of stable strontium in male adult RVH hooded rats. The rats (12/group, starting weight of 250 g) were fed ad libitum a standard laboratory diet and divided into four groups, which were administered 0.002, 900, 1900 or 3400 ppm strontium chloride (55% strontium) in their drinking water for 3 years. Assuming that an adult rat consumes water at a rate of 49 mL/day, the experimental doses correspond to 70, 147 and 263 mg/kg Sr/day. The control and experimental groups received adequate amounts of calcium (0.35 ppm) and magnesium (0.0682 ppm) in their drinking water. The animals were weighed and examined weekly. Histologic examinations of bone and observation of body weight changes in rats receiving strontium in drinking water revealed no abnormalities (Skoryna and Fuskova, 1981). The animal tissues from different organs (kidney, lungs, adrenal, brain, heart and muscle) were examined on gross and histologic levels. No evidence of changes in morphology was

observed; organs were not weighed. The concentration of strontium in tissues was determined by heated graphite atomization. In addition, strontium levels in the animals' serum were analyzed by standard atomic absorption spectrophotometry. Except for bone, no organ predilection for strontium was observed in either group. A chronic NOAEL of 263 mg/kg-day was identified from this study.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 300 includes 10 for species-to-species extrapolation and 10 for an incomplete database (including a lack of developmental and reproductive data) and to account for uncertainties in using data for strontium carbonate to derive a risk estimate that may apply to other salts of strontium. An uncertainty factor of 3 was applied for sensitive subpopulations; a factor of 10 was not warranted because the critical study was performed in young animals, a recognized sensitive subpopulation.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Pertinent data to derive an oral RfD based on the toxicity of stable strontium in humans were not located in the available literature. Estimates of dietary strontium intake range from 0.98-2.2 mg/day for adults, with milk providing about one-third of this (Snyder et al., 1975). Absorption of strontium from the gastrointestinal tract varies greatly, ranging from 9-63% (average of 38%) (Snyder et al., 1975). The bioavailability of strontium was estimated to be 20% in 6 healthy adult males administered 2.5 mmol of strontium chloride (Leeuwenkamp et al., 1990). Deficiency of dietary calcium leads to an increased absorption of strontium (Stokinger, 1981).

Use of strontium in the treatment of patients with osteoporosis has been reported. McCaslin and Janes (1959) reported treating 72 patients with daily doses of 1.7 g strontium (as strontium lactate) for periods ranging from 3 months to 3 years. Of the 32 patients who were available for follow-up, 84% experienced marked improvement. Assuming an average body weight of 70 kg, the supplementation to these patients was about 24 mg Sr/kg/day. Skoryna (1981) also reported subjective improvement in patients with osteoporosis receiving 274-1750 mg Sr/day as the gluconate, carbonate or lactate. No adverse side effects were reported in either study. Although these cases have been reported, strontium is not recognized as a standard therapy for osteoporosis (Krane, 1977).

Ingested strontium is distributed in the body in three compartments: plasma extracellular fluid; soft tissue and superficial zone of bone tissue; and bone itself (El Solh and Rousselet, 1981). The average adult is estimated to have a body burden of 320 mg strontium, 99% of which is in the

bones (Snyder et al., 1975; Stokinger, 1981). The toxic effect of excessive strontium intakes is inhibition of calcification of epiphyseal cartilage and deformities of long bones at high doses. Strontium causes adverse effects on bone by substituting for calcium in the hydroxyapatite crystal during bone calcification or by displacing calcium from existing calcified matrix (Skoryna, 1984; Kshirsagar, 1985).

As opposed to calcium, which is under homostatic regulation, strontium appears to be passively absorbed (Comar and Wasserman, 1964). However, several factors may affect the bioavailability of ingested strontium, for example, age and species, the form of strontium, and the composition of the diet, especially with regard to phosphorus, vitamin D and calcium levels. These factors are reviewed in U.S. EPA (1990, 1992).

The adequacy of calcium nutrition is a critical factor regarding strontium toxicity; rachitic changes are exacerbated by inadequate calcium levels (El Solh and Rousselet, 1981). The effect of dietary calcium on strontium toxicity was also demonstrated by Engfeldt and Hjerquist (1969). Rachitic changes were observed in weanling Sprague-Dawley rats fed a diet containing 0.95% strontium (950 mg/kg-day) and "optimal" 0.69% calcium for 4 weeks. When dietary calcium was raised to 1.6%, no rachitic changes were seen at the same dose of strontium.

Because their bones are actively growing, young animals are more sensitive than adult animals to excessive strontium intakes. In addition to the information presented in the critical study (Storey, 1961), the greater sensitivity of young animals was also demonstrated by Storey (1962). Both young (50-70 g) and adult (200-250 g) rats of both sexes (strain not specified) were provided a diet containing 1.8% strontium as strontium carbonate. The exposure continued for up to 7 months with several interim sacrifices. After only 3 weeks of exposure, the young rats exhibited a "rachitic gait" with the most obvious changes occurring in the distal end of the femur and the proximal end of the tibia. The epiphyseal plate was reported to be "grossly widened" and the "metaphysis was a mass of soft white tissue." Conversely, it was 3 months before any change was observed in the adult rats, this being the appearance of fine traverse lines in the upper tibial metaphysis. The author goes on to portray significant differences in the effects seen in young animals vs. adults provided the same dietary concentration of strontium. Because young rats consume more food per kg body weight, it is difficult to ascertain how much more sensitive young animals would be at a dose adjusted on a mg/kg bw/day basis.

Relatively little information is available regarding the potential for developmental toxicity resulting from exposure to strontium. Pregnant female Wistar rats (3/group) were administered subcutaneous doses of 0, 25, 50, 100 or 200 mg/kg of strontium nitrate (10.3, 20.7, 41.4 or 82.8 mg Sr/kg/day, respectively) during gestational days 9-19 (Lansdown et al., 1972). No effects were seen on the size or body weight of fetuses, litter sizes or the number of resorption sites. Skeletons and zones of calcification were normal and no histologic changes were seen in soft

tissues. Although this study reported no teratogenic effects of strontium, the small number of dams exposed and fetuses examined preclude a definite evaluation of the results.

In addition to the information available in rats, Marie and Hott (1986) studied the effects of strontium on weanling mice. Eleven male C57BL/6J mice were provided with drinking water containing 0.27% strontium chloride from 21 to 50 days of age. Another group of 13 untreated mice served as controls. The dose of strontium was based on the earlier study by Marie et al. (1985), which determined this level of strontium to be effective in stimulating bone formation without affecting bone mineralization in rats. In mice, no significant effects were observed in bone formation parameters except an increase in the osteoid surface and a decrease in the number of osteoclasts involved in bone resorption. No effect was seen on total calcified bone volume.

Skeletal abnormalities have also been observed in dogs administered oral doses of strontium (1-3 g strontium phosphate/day) in conjunction with low levels of dietary calcium (Lehnerdt, 1910).

In addition to the effects exerted on bones, strontium can also physiologic processes such as heart and other skeletal muscle contraction, and ionic transport across red blood cell membranes and nerve cells (reviewed in U.S. EPA, 1990, 1992). However, these effects are reported following intravenous infusion of large doses of strontium, which is of questionable relevance to oral exposures.

Initially, the primary concern of most investigators was the retention and absorption of radioactive strontium from water and food sources. Radioactive strontium is generally used as a tracer element to evaluate toxicokinetic properties (absorption, distribution and excretion). The actual dose of radioactive strontium used for this purpose is frequently unreported. The kinetics of trace amounts of radioisotopes and of stable isotopes, which are usually administered in much higher quantities, may differ.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

Confidence in the critical studies is rated as medium because together they determine the critical effect and suggest a sensitive population but have difficulties with incomplete reporting of experimental details (e.g., number of animals, experimental protocol). The database is rated as medium to low because although several studies exist to support these critical studies, they are all in one species and little information is available on reproductive or developmental effects.

Also, little is known about the speciation of strontium (e.g., how the toxicity of $SrCO_3$ relates to other strontium compounds). The confidence in the RfD is medium, reflecting the confidence in the study and the database.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1990, 1992

Agency Work Group Review — 07/18/1991, 06/23/1992

Verification Date — 06/23/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Strontium conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Strontium
CASRN — 7440-24-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Strontium
CASRN — 7440-24-6

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Strontium
CASRN — 7440-24-6

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Strontium
CASRN — 7440-24-6

Date	Section	Description
10/01/1992	I.A.	Oral RfD summary on-line
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Strontium
CASRN — 7440-24-6

- 7440-24-6
- strontium
- stable strontium
- HSDB 2545