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Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Samarium Chloride
(CASRN 10361-82-7)

and

Stable (Nonradioactive) Samarium Nitrate
(CASRN 10361-83-8)

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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR STABLE (NONRADIOACTIVE) SAMARIUM CHLORIDE (CASRN 10361-82-7) AND STABLE (NONRADIOACTIVE) SAMARIUM NITRATE (CASRN 10361-83-8)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Samarium (Sm; CASRN 7440-19-9) is a rare earth element belonging to the lanthanide[1] series of the periodic table. Samarium compounds are used in carbon-arc lamps for movie projection, permanent magnets, organic reagents, lasers, and alloys. Samarium can form water-soluble compounds (e.g., samarium chloride and samarium nitrate) and insoluble compounds (e.g., samarium oxide and samarium hydroxide). Water-soluble samarium compounds (e.g., samarium chloride) can form insoluble hydroxides at neutral or alkaline pH. In general, the lanthanides can be radioactive or stable. This PPRTV document addresses only the toxicity of stable forms of samarium and its compounds, and derives toxicity values only for samarium chloride and samarium nitrate. Samarium chloride and samarium nitrate are typically found as the hexahydrates (CASRN 13465-55-9 and 13759-83-6, respectively).

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (U.S. EPA, 2009) does not list an oral reference dose (RfD), inhalation reference concentration (RfC), or cancer assessment for stable, nonradioactive samarium or samarium compounds. Subchronic or chronic RfDs or RfCs for samarium are not listed in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). No relevant documents are included in the Chemical Assessment and Related Activities (CARA) list (U.S. EPA, 1991, 1994).

The Agency for Toxic Substances and Disease Registry (ATSDR, 2009), the International Agency for Research on Cancer (IARC, 2009), the National Toxicology Program (NTP, 2005, 2009) and the World Health Organization (WHO, 2009) have not reviewed the toxicity or carcinogenicity of samarium. The American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health

[1]The term "lanthanides" refers to 15 elements with atomic numbers 57 through 71: lanthanum, cerium, praseodymium, neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, and lutetium. The term "rare earths" refers to the lanthanide series plus yttrium (atomic number 39) and scandium (atomic number 21) (Kirk-Othmer, 1995).

(NIOSH, 2005), and the Occupational Safety and Health Administration (OSHA, 2009) have not established occupational exposure limits for samarium. One toxicological review of the lanthanides has been located that derived toxicity values for several lanthanides—but not for samarium or its compounds (TERA, 1999).

Literature searches for studies relevant to the derivation of provisional toxicity values for samarium (CASRN 7440-19-9) were conducted in June 2007 in MEDLINE, TOXLINE special, and DART/ETIC (1960s−June 2007); BIOSIS (2000−June 2007); TSCATS/TSCATS2, RTECS, CCRIS, HSDB, and GENETOX (not date limited); and Current Contents (previous 6 months). These literature searches were updated in October 2008 and July 2009. The latter search identified an additional subchronic study (Weilin et al., 2006) as well as studies of rare earth complexes as potential anticancer treatments (Kostova et al., 2008, 2007, 2005), which have been incorporated into the document. Reviews of rare earth or lanthanide toxicity (Haley, 1991; TERA, 1999; Wells and Wells, 2001) also have been consulted for pertinent information.

REVIEW OF PERTINENT LITERATURE

Overview of Rare Earth Chemical Properties

Environmental and occupational exposure to samarium occurs along with exposure to other lanthanide and rare earth compounds, including some radioactive isotopes. The lanthanide series of elements, and the rare earths yttrium and scandium, differ little with regard to chemical properties (Kirk-Othmer, 1995), and they are difficult to physically separate from one another. Kirk-Othmer (1995) and Wells and Wells (2001) reviewed the physical-chemical properties of the lanthanides. These reviews indicate that elements in this series are highly reactive, have high melting points, ignite in air, and are active reducing agents. Many of the properties of these compounds are associated with a phenomenon known as lanthanide contraction, wherein the radius of ions in the series decreases with atomic number due to the configuration of the outer electron shell. This results from an increasing positive charge on the nucleus with increasing atomic number. Solubility also increases with increasing atomic number. Wells and Wells (2001), in general, contend that toxicity is inversely related to atomic number and solubility. The rare earth elements are broadly grouped into "light" (La, Ce, Pr, Nd, Sm, Eu, and Gd) and "heavy" (Y, Tb, Dy, Ho, Er, Tm, Yb, and Lu) classes (Wells and Wells, 2001); samarium belongs to the light lanthanide group. For any given lanthanide, soluble forms include chlorides, nitrates and sulfates, while insoluble forms include carbonates, phosphates and hydroxides. The larger, lighter (smaller atomic number) and less soluble ions have been observed to deposit primarily in the liver, while the smaller, heavier (larger atomic number) and more soluble ions are similar in ionic radius to divalent calcium and distribute primarily to bone (Wells and Wells, 2001). Due to an isoelectric point at a pH <7, lanthanides precipitate readily at physiological pH.

Human Studies

Human studies have indicated an association between occupational exposure to rare earths and the occurrence of pneumoconiosis and progressive pulmonary fibrosis (Wells and Wells, 2001; Palmer et al., 1987). Because distinguishing individual lanthanides is analytically challenging, it is has been difficult to discern the effects of the individual

lanthanides, both in human cases and animal studies. In addition, the co-occurrence of radioactive lanthanides[2], thorium isotopes[3], and silica dust has complicated the interpretation of toxicity—especially with regard to human exposures (Palmer et al., 1987).

Human toxicity data on samarium were limited to case reports of pneumoconiosis and progressive pulmonary fibrosis in workers exposed to airborne mixtures of rare earth compounds, including lanthanum, cerium, neodymium, samarium, praseodymium, terbium, yttrium, lutetium, and europium, in the air (Sulotto et al., 1986; Kappenberger and Buhlmann, 1975; Husain et al., 1980; Sabbioni et al., 1982; Vocaturo et al., 1983; Colombo et al., 1983; Vogt et al., 1986; Waring and Watling, 1990; and Deng et al., 1991). In these case reports, rare earth pneumoconiosis has been characterized by pulmonary interstitial infiltrates, peribronchial and perivascular lesions, and, in some cases, impaired pulmonary function, dyspnea, cyanosis, and pulmonary fibrosis (Palmer et al., 1987; Wells and Wells, 2001). The workers in these studies were exposed to fumes generated by carbon-arc lamps used in movie projection, flood-lighting, printing, photo-engraving, lithography, and electrowelding (Palmer et al., 1987). Such metal fumes generally are very small particles of metal oxides that would not be representative of rare earth dusts generated by mechanical means.

The case reports generally detailed the pulmonary findings of individuals, so there was no information on population exposures or health effects. Haley (1991) reviewed the case studies and concluded that the studies were limited by inadequate documentation of work histories and worker health. None of the case reports provided any quantitative measures of exposure (e.g., concentrations of airborne particulates or individual rare earth elements in the areas of exposure). In addition, the components of rare earth mixtures to which workers were exposed were not consistent, nor were the medical histories or details of diagnosis and medical follow-up. Interpretation of the human cases also is confounded by possible exposures to silica dust, radioactive rare earths[4], and α-emitting contaminants, such as thorium[5], that were present in the occupational setting and have been associated with pneumoconiosis (Palmer et al., 1987). Haley (1991) proposed that the pneumoconiosis or fibrosis could have resulted from either an inflammatory response to the dust itself, or irradiation of tissues. However, Haley (1991) indicated that there was little evidence for a significant contribution from radioactive contaminants. Palmer et al. (1987) concluded that inhalation exposure to high concentrations of stable rare earths could produce lesions consistent with pneumoconiosis and progressive pulmonary fibrosis, and that the potential for inducing these lesions was related to chemical type, physiochemical form, airborne concentration, and exposure duration.

Although there is evidence for an association between human inhalation exposure to rare earth elements and pneumoconiosis or fibrosis, the relative contribution of samarium (or any other individual element) to the development of pneumoconiosis has not been established.

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[2]Lanthanide and rare earth isotopes occur as a result of radioactive decay and by nuclear reactions involving neutron bombardment (Kirk-Othmer, 1995). The primary decay modes for the radioactive isotopes of the rare earths involve β (including electron capture), γ, and X-ray emissions. ^{149}Terbium and ^{151}terbium also have α-decay modes with half-lives ranging from 4 to 18 hours (ICRP, 1983).

[3]Primary decay mode involves α-emissions.

[4]Having primarily β, γ, and X-ray decay modes.

[5]Thorium 229 has an alpha-decay mode with a half-life of 7340 years; Thorium 226 has an alpha-decay mode with a half-life of 31 minutes (ICRP, 1983).

Furthermore, the available human case studies contained no dose-response information that could be used to develop provisional toxicity values for any of the stable nonradioactive lanthanides.

Animal Studies

Oral Exposure—Samarium and Compounds

Haley et al. (1961) fed groups of six male and six female rats (strain not reported) 0, 0.01, 0.1, or 1% samarium chloride (99% pure) in food for 12 weeks. Compound intake is estimated to be 9.1, 91, or 908 mg/kg-day (5.3, 53, or 532 mg Sm/kg-day) in the males, and 10.0, 100, or 1001 mg/kg-day (5.9, 59, or 586 mg Sm/kg-day) in the females. These doses[6] have been calculated using estimated average body weights of 240 g for males and 180 g for females[7], and estimated food consumption rates of 0.0218 kg/day for males and 0.0180 kg/day for females (U.S. EPA, 1988). Body weight was measured biweekly throughout the samarium chloride study; hematology, including total erythrocytes, total leucocytes, differential cell count, hemoglobin, and hematocrit, and histology, including heart, lung, liver, kidney, pancreas, spleen, adrenal, and small intestine, were assessed at the end of the study. No exposure-related histopathological or other changes were observed in either gender, yielding a NOAEL of 908 mg/kg-day for samarium chloride (532 mg Sm/kg-day) in males and 1001 mg/kg-day for samarium chloride (586 mg Sm/kg-day) in females, with no lowest-observed-adverse-effect level (LOAEL). The tabular data suggests there was a slight decline in leukocyte counts among treated rats. However, the very wide reported variability and the fact that Haley et al. (1961) cited Gardner (1947) in concluding the counts were within the reported normal range for rats, lead to a conclusion that the changes were not significant. Haley et al. (1961) suggested that the lack of observed effects might have resulted from poor absorption of the chloride following oral administration.

Weilin et al. (2006) treated groups of eight male and eight female Sprague-Dawley rats with 0-, 3-, 4.5-, and 6-mg samarium nitrate per liter of drinking water for 5 months. Data for males and females were not distinguished. Averaging the default water intake factors for male (0.139 L/kg-day) and female (0.152 L/kg-day) from U.S. EPA (1988), compound intakes are estimated to be 0.438, 0.657, and 0.876 mg $(SmNO_3)_3$/kg-day. Using atomic weight data for samarium (150 g/mole), nitrogen (14 g/mole), and oxygen (16 g/mole), these represent ingestion rates of approximately 0.196, 0.294, and 0.392 mg Sm/kg-day. At sacrifice, Weilin et al. (2006) measured body weight; liver, kidney, lung and pancreas weights; and superoxide dismutase (SOD) activities and malondialdehyde (MDA) concentrations in liver and kidney tissues. Table 1 summarizes the body and organ weight data reported, while Table 2 summarizes the SOD and MDA data. The high variability of body-weight data makes its interpretation difficult. However, only the high dose appears to have had any effect on body weight. Relative liver weights were statistically significantly ($p < 0.05$) greater among high dose animals, but this increase of <7% was not biologically meaningful. Kidney weight data exhibited no apparent dose-response trend and differences between dose groups were statistically insignificant ($p > 0.05$). Both lung and pancreas relative weights exhibited dose-related increases among low

[6]Dose in mg/kg-day = dietary concentration in mg/kg diet × food consumption rate in kg diet/day ÷ body weight in kg, where food consumption rate = 0.026 kg/day for males and 0.020 kg/day for females.

[7]Body weights for samarium-treated animals were not reported in the study. For the purpose of dose estimation, body weights were estimated from a companion study of gadolinium chloride reported in the same paper. Haley et al. (1961) indicated that growth curves for samarium-treated animals were almost identical to those observed for gadolinium chloride.

and mid-dose rats; among high dose rats, these relative organ weights were significantly ($p < 0.05$) greater than controls, but less than those reported among mid-dose rats. SOD activities in liver and kidney tissues exhibited slight dose-related decreases. MDA concentrations in liver and kidney tissues both exhibited dose-related increases, and increased liver MDA concentrations were statistically significant ($p < 0.05$) at all doses. These data suggest a 5-month LOAEL of 0.438 mg $(SmNO_3)_3$/kg-day or 0.196 mg Sm/kg-day, with no NOAEL, for increased relative pancreas and lung weights, and increased MDA concentrations in liver tissues of male and female SD rats.

Table 1. Body Weight and Organ/Body-Weight Ratios of Sprague-Dawley Rats Treated with Samarium Nitrate in Drinking Water

Dose[a]	*N*	Body (grams)	Liver/Body	Kidney/Body	Lung/Body	Pancreas/Body
0	16	495 ± 158	30 ± 2	6.1 ± 0.5	3.07 ± 1.41	1.32 ± 0.53
0.44	15	494 ± 170	32 ± 3	5.8 ± 0.5	3.91 ± 0.55	1.76 ± 0.29
0.66	15	485 ± 127	31 ± 4	6.1 ± 0.5	4.91 ± 0.39	1.98 ± 0.71
0.88	13	438 ± 144	32 ± 2	6.3 ± 0.6	4.28 ± 0.06	1.65 ± 0.04

[a]Eight males and eight females per dose group; Weilin et al. (2006), Table 1.

Table 2. Superoxide Dismutase (SOD) and Malondialdehyde (MDA) in Liver and Kidney Tissues of Sprague-Dawley Rats Treated with Samarium Nitrate in Drinking Water[a]

Dose[b]	*N*	Liver SOD[c]	Kidney SOD	Liver MDA[d]	Kidney MDA
0	16	3390 ± 438	1079 ± 236	115 ± 52	89 ± 34
0.44	15	3387 ± 611	1043 ± 92	137 ± 29	92 ± 25
0.66	15	3162 ± 367	1042 ± 130	146 ± 39	95 ± 26
0.88	13	3155 ± 568	1022 ± 185	152 ± 24	96 ± 23

[a]mg/kg-day, estimated from drinking water concentrations and standard water intake factors (U.S. EPA, 1988).
[b]Eight males and eight females per dose group; Weilin et al. (2006), Tables 2 and 3.
[c]μmol/ml.
[d]Nmol/g tissue.

Hu et al. (2007) treated ICR stain male mice with samarium nitrate in drinking water at concentrations of 0, 5, 50, 500, and 2000 mg/L for 3 months. Both the growth and fertilization rates of the mice presented a dose-related decline. There also was an "obvious" increase in the frequency of shortened bodies and tails among embryos produced by treated male mice. Further details, such as number of mice per group and other endpoints were not provided in the abstract source for these data.

Chen et al. (2005) treated male mice with samarium nitrate in drinking water containing 0, 4, 20, 100, and 500mg/L for 3 months. The weight of body and main organs, and the enzyme activity of LDH, ACP, ALP, and ATP in testis were determined. Gross testicular effects were reported in the 20mg/L- and 100mg/L-dose groups; LDH enzyme activity was inhibited in

100mg/L- and 500mg/L-dose groups; and LDH enzyme activity exhibited a dose-response relationship; but the ACP enzyme activity was not influenced. Three kinds of ATP enzyme activity all were "promoted weakly and inhibited strongly" with increase of samarium concentration. Further details, such as number of mice per group, were not provided in the abstract source for these data.

Oral Exposure—Rare Earth Mixtures

Due to their limited gastrointestinal absorption, Hutcheson et al. (1975) hypothesized that heavy metal oxides could be used as markers to measure nutrient intake and utilization in studies with animals or humans. To determine whether these chemicals could be used safely for this purpose, Hutcheson et al. (1975) investigated the toxicity of a mixture of lanthanides, including oxides of lanthanum, samarium, europium, terbium, dysprosium, thulium, and ytterbium, and other metals, including scandium oxide, chromium oxide, and barium sulfate, in a 3-generation dietary study with CF-1 mice. Groups of 16 female and 8 male weanlings of each generation were continuously fed diets containing these metals at 0, 1, 10, 100, or 1000 times (X) the amounts proposed for use as markers of dietary intake and utilization. The proposed dietary marker amount (X) for each chemical was one-fifth of the concentration necessary for estimation by neutron-activation analysis[8] with an error of 5%. Table 3 shows the concentrations measured in basal (control) diets and test diets. The 1000X diet was not analyzed for metal content; Hutcheson et al. (1975) reported the metal concentrations in the 1000X diets as 10 times that of the measured concentrations in the 100X diet.

Table 3. Measured Concentrations of Rare Earth Elements in Control and Test Diets[a]

Element[b]	Concentration of Element in Diets (mg/kg diet)				
	Control	1X[c]	10X	100X	1000X[d]
Europium (Eu)	0.04 ± 0.02[e]	0.08 ± 0.02	0.32 ± 0.02	2.10 ± 0.02	21.0
Samarium (Sm)	0.33 ± 0.02	1.64 ± 0.13	11.11 ± 1.71	108.00 ± 2.00	1080.0
Lanthanum (La)	0.69 ± 0.02	1.16 ± 0.22	6.08 ± 1.02	62.50 ± 1.20	625.0
Dysprosium (Dy)	0.25 ± 0.02	1.44 ± 0.07	11.38 ± 0.74	102.50 ± 2.50	1025.0
Ytterbium (Yb)	0.05 ± 0.02	0.19 ± 0.02	1.12 ± 0.08	12.00 ± 0.30	120.0
Scandium (Sc)	0.12 ± 0.01	0.22 ± 0.01	1.58 ± 0.08	13.30 ± 0.50	133.0
Terbium (Tb)	0.02 ± 0.01	0.80 ± 0.06	11.02 ± 1.95	79.95 ± 4.25	799.5

[a]Hutcheson et al. (1975).
[b]Concentrations of Tm, Cr, and Ba were not measured in control or test diets.
[c]1X refers to 1 times the amounts proposed for use as nutritional markers (nominal 1X concentrations: Eu = 0.036 ppm; Sm = 0.80 ppm; La = 0.40 ppm; Dy = 1.20 ppm; Yb = 0.12 ppm; Sc = 0.12 ppm; Tb = 1.20 ppm; Tm = 0.08 ppm; Cr = 0.02 ppm; and Ba = 0.008 ppm).
[d]Concentrations of elements in the 1000X were not measured. Study authors estimated concentrations as 10 times higher than those in the 100X diet.
[e]Means ± SE of 5 samples.

[8]Neutron bombardment creates traceable radioactive forms of the various compounds after the experiment is terminated.

Hutcheson et al. (1975) reported neither dose nor food intake during the study. Therefore, daily doses of samarium and other rare earths have been calculated for this review using the average body weight of mice prior to mating, reported by Hutcheson et al. (1975) as 0.029 kg, and food consumption estimates, based on a U.S. EPA (1988) allometric equation relating food consumption (kg food/day) to body weight (kg) for laboratory mammals. Table 4 presents the estimated doses. Study endpoints included mortality, clinical signs, body weight (all adults prior to mating and dams at weaning), morphological development, reproductive outcome (number of females having litters and average litter size), neonatal growth during lactation (pup weaning weight), and pup growth after lactation (pup body-weight gain from 3 to 6 weeks of age). At 3 months of age in each generation, Hutcheson et al. (1975) collected blood from 5 mice/group in the control and 100X groups and analyzed it for hematology, including red and white blood cell counts, red blood cell size, hemoglobin concentration and hematocrit, and serum proteins and globulins. Gross pathological examinations were performed on five mice per group of third generation adult mice receiving control and 100X diets, but no histopathological examinations were performed on any animals in the study (Hutcheson et al., 1975).

Table 4. Estimated Doses for Mice Fed Rare Earth Elements in the Diet[a]

Element[c]	Dose (mg/kg-day)[b]				
	Control	1X	10X	100X	1000X
Europium (Eu)	0.007	0.014	0.058	0.380	3.8
Samarium (Sm)	0.06	0.29	2.0	19.6	195.5
Lanthanum (La)	0.125	0.210	1.101	11.32	113.1
Dysprosium (Dy)	0.045	0.261	2.060	18.56	185.6
Ytterbium (Yb)	0.009	0.034	0.203	2.17	21.7
Scandium (Sc)	0.022	0.040	0.286	2.41	24.1
Terbium (Tb)	0.004	0.145	1.995	14.47	144.7
Total Lanthanides	0.27	0.99	7.7	69	690

[a]Hutcheson et al. (1975).
[b]Dose (mg/kg-day) = Concentration in food (mg/kg food) × 0.00525 kg food/day ÷ 0.029 kg bw.
[c]Concentrations in food are from Table 1.

Hutcheson et al. (1975) reported the overall incidence of morbidity and mortality as <0.5%; data on mortality or clinical signs of toxicity were not reported for individual test groups or generations of mice. Differences in body weights of treated mice from matched controls were not statistically significant for all generations prior to mating and dams prior to weaning. Compared to matched controls, no treatment-related effects on pup body weight at the end of weaning were observed in any generations. Table 5 summarizes pup body-weight gains during Weeks 3 to 6 for each generation. In the first generation, body-weight gains were significantly decreased in the 1X, 10X, and 100X groups compared to controls, but they were similar to controls in the 1000X group. In the second generation, body-weight gains were significantly increased in the 1X group and significantly decreased in the 100X and 1000X groups compared to controls, but similar to controls in the 10X group. In the third generation, body-weight gains were significantly decreased compared to controls in the 100X group and were similar to

controls in the 1X, 10X, and 1000X groups. Hutcheson et al. (1975) concluded that the observed body-weight gain patterns were not consistently associated with dietary concentrations of the mixture, and a correlation analysis performed for this report confirmed this conclusion.

Table 5. Average Daily Weight Gain in CF-1 Mouse Pups Fed a Rare Earth Mixture in Diet from 3 Weeks to 6 Weeks of Age[a]

Generation	Weight Gain (g)				
	Control	1X	10X	100X	1000X
First	0.200 ± 0.009[b]	0.106 ± 0.010[c]	0.108 ± 0.012[c]	0.134 ± 0.013[c]	0.230 ± 0.014
Second	0.296 ± 0.013	0.360 ± 0.010[c]	0.328 ± 0.017	0.207 ± 0.007[c]	0.211 ± 0.009[c]
Third	0.258 ± 0.012	0.286 ± 0.017	0.250 ± 0.011	0.133 ± 0.006[c]	0.280 ± 0.012

[a]Hutcheson et al. (1975).
[b]Mean ± SE.
[c]Significantly different matched control ($p < 0.01$).

Dependence of mean weight gain on dosage was tested using Pearson and Spearman (rank) correlation coefficients as the test statistics. Weight gain was not significantly dependent on dose. Pearson: F_1 $p = 0.16$; F_2 $p = 0.25$; F_3 $p = 0.68$; Spearman: F_1 $p = 0.42$; F_2 $p = 0.23$; F_3 $p = 0.69$.

Hutcheson et al. (l975) observed no effects on hematology or clinical chemistry parameters in the 100X group, but did not examine other treated groups for these endpoints. No effects on reproductive parameters or morphological development were observed. Necropsy performed on third generation control and 100X mice revealed no abnormal findings. Hutcheson et al. (l975) observed no effects on body-weight gain or survival in the 1000X group; however, clinical chemistry, hematology, and necropsies were not conducted for this treatment group. As such, the highest dose group cannot be designated as a NOAEL. The 100X treatment (69 mg/kg-day of the rare earth mixture) might be considered a freestanding NOAEL based on the parameters assessed. Reproductive effects observed in studies of some rare earths, including decreased pregnancy success, decreased litter size, and decreased neonatal weight (Wells and Wells, 2001) were not observed in this study. However, Hutcheson et al. (1975) did not evaluate blood coagulation, which is known to be affected by exposure to rare earths (Wells and Wells, 2001). The usefulness of this study for assessing samarium toxicity is limited by the coexposure to other rare earths. There is no information to assess how the various elements react together in a complex mixture or how the presence of other rare earths (as well as barium sulfate and chromium oxide) affects samarium pharmacokinetics or toxicity.

Inhalation Exposure—Samarium and Compounds

There were no inhalation studies of samarium or its compounds alone (without other rare earth compounds).

Inhalation Exposure—Rare Earth Mixtures

Studies investigating the effects of respiratory exposure to rare earth mixtures included a 14-day intratracheal study and a 3-year inhalation study in guinea pigs exposed whole body to mixtures containing several (insoluble) rare earth compounds, including fluorides and oxides of cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, germanium, thulium, ytterbium, and lutetium (Schepers, 1955a,b;

Schepers et al., 1955). In the study involving intratracheal instillation, a blend (termed the high-oxide blend) of carbon (31%), rare earth fluorides (39.6%), rare earth oxides (26.4%), and potassium sulfate (3%) was ground, suspended in isotonic saline and anodized. A 50-mg dose of the high oxide blend was administered twice (7 days between doses) to a group of 9 guinea pigs. A second blend (termed the high-fluoride blend) containing carbon (17.0 %) graphite (3.0%), rare earth fluorides (65.0%), rare earth oxides (10.0%), and potassium sulfate (5.0%) was prepared in a manner similar to the high oxide blend, and administered on the same schedule to a second group of 9 guinea pigs. The high fluoride blend was also administered as an aerosol via inhalation to a group of 75 guinea pigs 8 hours/day, 5½ days/week (44 hours/week), for 3 years. Schepers (1955a,b) and Schepers et al. (1955) did not report the concentrations of samarium or other rare earth constituents in the exposure mixtures, nor did they report the concentration of the mixture in the aerosol exposure chamber. Rather, they reported only that particle concentrations were "high" in the early weeks but "leveled off" to about 200,000 to 300,000 particles (1−2 micron diameter) per cubic foot of air.

Following intratracheal instillation, mortality was observed in three guinea pigs receiving the high-oxide blend (10−11 days postexposure) and in four guinea pigs receiving the high-fluoride blend (12−29 days postexposure). Schepers et al. (1955) considered the deaths to be treatment-related. Macroscopic evaluation of the lungs revealed changes consistent with deposition of inert material (congestion and consolidation with large single or multiple black-pigmented conglomerate lesions). Histologic evaluation (Schepers, 1955b) of survivors exposed to the high-oxide dust for up to a year revealed focal aggregation of the dust (cellular eosinophilia) but no chronic cellular reaction or fibrosis. Schepers (1955b) noted similar dust deposits in the animals exposed to the high-fluoride blend but these animals developed transient chemical pneumonitis, subacute bronchitis, and bronchiolitis. As with the other blend, Schepers (1955a) observed no fibrosis or granulomatosis.

Following long-term inhalation exposure to the high-fluoride blend of rare earths, the histopathological changes observed in guinea pigs included focal hypertrophic emphysema, regional bronchiolar structuring, and subacute chemical bronchitis. Schepers (1955a) noted that, as with the intratracheal instillation studies, pigment was deposited and retained in foci. In contrast to human occupational exposure cases, no fibrosis or granulomatosis was observed.

The results of this study do not corroborate conclusions drawn by Palmer (1987) that chronic occupational exposure to stable rare earth dusts results in progressive pulmonary fibrosis in humans. However, the exposures in the animal and human studies were not strictly comparable due to differences in exposure components, including the presence of silica dust, radioactive rare earths, and thorium in the human exposures. Further, as noted by Palmer (1987), other factors that may explain the differences in human and animal findings include chemical type, physiochemical forms, doses, and durations of exposure. In any case, the relevance of studies by Schepers (1955a,b; Schepers et al., 1955) to samarium toxicity is uncertain due to the lack of information on specific exposure concentrations and the samarium content of the mixtures.

Other Studies

Acute Exposure

Acute Lethality Studies—Acute oral lethality studies have been conducted for samarium nitrate and samarium chloride (see Table 6). Bruce et al. (1963) reported an oral LD_{50} of 901 mg Sm/kg following gavage administration of samarium nitrate (50% aqueous solution) in adult female Sprague-Dawley rats observed for 30 days after exposure. Haley et al. (1961) was not able to determine an acute LD_{50} for samarium chloride in CF1 mice (age, weight, and gender not reported) because no mortalities occurred up to 7 days after oral exposure (method of administration not reported) at the highest dose tested (1172 mg Sm/kg); higher doses were not be evaluated due to solubility limits.

Table 6 summarizes data from the intraperitoneal acute lethality studies that have been conducted for samarium chloride, nitrate, citrate, and edetate compounds. For samarium chloride, LD_{50}s ranged from 214 mg Sm/kg in CFW albino mice (gender not reported) (Graca et al., 1962) to 343 mg Sm/kg in male CF1 mice (Haley et al., 1961). Haley et al. (1961) observed clinical signs of toxicity in mice following intraperitoneal (i.p.) treatment with samarium chloride, including decreased respiration, lethargy, muscle spasms, abdominal cramps, and diarrhea; dose-response data were not reported. In mice administered samarium chloride, i.p., precipitate was observed at the injection site, indicating that absorption was incomplete (Graca et al., 1962). For samarium nitrate, Bruce et al. (1963) reported similar intraperitoneal LD_{50}s in female Sprague-Dawley rats (96 mg Sm/kg) and female CF1 mice (106 mg Sm/kg).

Table 6. Acute Lethality of Stable Samarium Compounds Following Oral and Parenteral Exposure

Compound	Species/Strain (Gender)	Route of Exposure	LD_{50} (mg/kg body weight)[a]	Reference
Samarium chloride	Mice/CF1 (NR)	oral (not specified)	For $SmCl_3$: >2000 For Sm: >1172	Haley et al. (1961)
	Mice/CFW albino (NR)	i.p.	For $SmCl_3$: 365[b] For Sm: 214	Graca et al. (1962)
	Mice/CF1 (male)	i.p.	For $SmCl_3$: 585 (508.7−672.7) For Sm: 343	Haley et al. (1961)
Samarium nitrate	Rats/Sprague-Dawley (female)	oral (gavage, 50% aqueous solution)	For $Sm(NO_3)_3$: 2900 (2660−3161) For Sm 901 (890−1069)	Bruce et al. (1963)
	Mice/CF1 (female)	i.p.	For $Sm(NO_3)_3$: 315 (258−384) For Sm: 106 (87−130)	Bruce et al. (1963)
	Rats/Sprague-Dawley (female)	i.p.	For $Sm(NO_3)_3$: 285 (254−319) For Sm: 96 (86−108)	Bruce et al. (1963)
	Rats/Sprague-Dawley (female)	i.v.	For $Sm(NO_3)_3$: 35.8 (27.3−49.9) For Sm: 13.0 (9.9−18.1)	Bruce et al. (1963)
	Rats/Sprague-Dawley (male)	i.v.	For $Sm(NO_3)_3$: 59.1 (40.5−86.3) For Sm: 20.0 (13.7−29.2)	Bruce et al. (1963)

[a](): 95% confidence limits, as reported by study authors
[b]Precipitate observed at injection site.

NR = not reported; i.p. = intraperitoneal injection; i.v.: intravenous injection

Graca et al. (1962) tested the acute lethality of samarium in citrate and edetate complexes. The test materials were described as "chloride-citrate" and edetate complexes or chelates; however, the exact nature and molecular formula or weight were not given. The chelating agents were added to enhance the solubility of the chloride and prevent injection-site precipitation. Graca et al. (1962) reported i.p. LD_{50}s in equivalent units of mg $SmCl_3$/kg, rather than in terms of the compound tested or in equivalent dose of the rare earth alone; it is not clear from the study if this was a reporting error, if the units were converted to $SmCl_3$ equivalents, or if all the test materials were complexes of samarium chloride. As a consequence of this uncertainty, the LD_{50}s reported by Graca et al. (1962) are not considered to be reliable indicators of the acute toxicity of the citrate and edetate compounds. As reported by Graca et al. (1962), i.p. LD_{50}s for samarium citrate complexes were 164.25 mg $SmCl_3$/kg in CFW albino mice (age and gender not reported) and 74.8 mg $SmCl_3$/kg in guinea pigs (age, strain, and gender not reported); for samarium edetate complexes, LD_{50}s were 311.18 mg $SmCl_3$/kg in CFW albino mice and 177.95 mg $SmCl_3$/kg in guinea pigs Graca et al. (1962). These LD_{50}s should be interpreted cautiously, given the uncertainties outlined above.

Bruce et al. (1963) reported intravenous LD_{50}s of 20 and 13 mg Sm/kg for samarium nitrate in male and female Sprague-Dawley rats, respectively. Bruce et al. (1963) also tested the hypothesis that the nitrate ion might be the source of toxicity and found it was not: no effects were observed among 10 female rats within 30 days of i.p. injection of 181 mg/kg sodium nitrate. Wells and Wells (2001) questioned the validity of intravenous acute lethality data for rare earth compounds because mortality after exposure to intravenously-administered rare earths has exhibited a bell-shaped dose-response curve that may be due to the formation of rare earth colloids in the blood at high doses of the chloride or nitrate compounds.

The acute lethality data are of limited utility for comparing the relative toxicity of different samarium compounds. As noted earlier, the available LD_{50}s for edetate and citrate forms of samarium (Graca et al., 1962) cannot be considered reliable due to uncertainty in the reported doses. The intravenous lethality data also are questionable due to presumed formation of colloids in the blood after intravenous administration of high doses of the chlorides and nitrates. Acute i.p. lethality data for samarium chloride in mice, and samarium nitrate in mice and rats suggest that the acute i.p. toxicity of these samarium compounds is of comparable order of magnitude; LD_{50}s ranged between 106 and 343 mg Sm/kg. It should be noted that the one mouse i.p. LD_{50} for samarium nitrate is for female mice (Bruce et al., 1963), while the LD_{50}s for samarium chloride are for male mice (Haley et al., 1961) or for mice of unspecified gender (Graca et al., 1962). Because gender differences in the acute lethality of some rare earth compounds has been noted (Bruce et al., 1963; Wells and Wells, 2001), comparisons between these LD_{50}s is of limited utility for evaluating relative toxicity of the different compounds. In addition, since precipitate was observed at the injection site in one of the mouse acute lethality studies of samarium chloride (Graca et al., 1962), the absorption of samarium chloride may have been affected by the formation of insoluble hydroxides or protein complexes at the injection site.

The oral acute toxicity data for samarium chloride and samarium nitrate are not comparable, primarily because the studies were conducted in different species, and species differences in absorption or toxicity could not be ruled out without additional data collection. Wells and Wells (2001) reported that the nonmetallic components of rare earth compounds may strongly influence a compound's acute toxicity. Greater oral toxicity of the samarium nitrate might be inferred from the properties of the nitrate anion, if hydrolysis of the nitrate anion in the

stomach leads to the formation of reactive nitrogen compounds such as nitric oxides, nitrous suboxides, and nitric acid in the gastrointestinal tract. However, the behavior of samarium nitrate in the gut has not been studied, and available data do not support potential conclusions that the nitrate anion causes the observed differences in relative oral toxicities of the nitrate and chloride forms of samarium.

Data on the acute oral or parenteral toxicity of insoluble samarium compounds (e.g., oxides or hydroxides) have not been located. While an assessment of the behavior of these compounds in the gastrointestinal milieu (e.g., dissociation in the stomach and/or small intestine) might provide some insight into the oral absorption of these compounds, few conclusions regarding their relative acute toxicities can be drawn in the absence of corresponding parenteral toxicity data. As with the nitrate form, the potential for formation of reactive species in the gut upon dissociation of the oxide or hydroxide forms provides a mechanistic basis for potentially greater toxicity, but this has not been studied.

Other Acute Studies—Graca et al. (1964) investigated the effects of acute intravenous exposure to chloride, citrate, and edetate compounds of rare earth elements on heart rate, blood pressure, respiration, and clinical hematology in male and female dogs (breed, number, and gender not specified). Aqueous solutions of 15 rare earth elements, equivalent to 5% of the chloride, of 15 rare earth elements were injected into a cannula inserted into the left femoral vein. Ten doses of 10 mg/kg each, as the chloride or its equivalent in the chelates, were injected into anesthetized dogs at 10-minute intervals. For each rare-earth element, groups of three dogs were treated with the chloride, citrate, or edetate. Three groups of control dogs were injected with sodium citrate (n = 6), ammonium edetate calcium (versenate) (n = 6) or Ringer's solution (n = 12) in the same manner as treated animals. Blood samples were collected from the right femoral vein before treatment and 0, 10, 30, 60, 100, and 160 minutes after treatment for analysis of erythrocyte, leukocyte, and differential cell counts; prothrombin and coagulation time; hemoglobin; sedimentation; and hematocrit. After 160 minutes, the animals were necropsied and tissues were collected for histopathology (liver, spleen, kidney, lung, sternum, mesentery lymph nodes, heart, adrenal, and ovaries or testes). Heart rate, respiration, and blood pressure were measured at the same intervals as blood samples.

Graca et al. (1964) generally discussed results for the 15 rare earth elements and presented them graphically as change over time after treatment. No statistical analysis for any endpoint was provided in the report and insufficient details are provided to allow such analyses for this report. Graca et al. (1964) reported that 14/45 dogs injected with chlorides, 4/45 injected with citrates, and 1/45 injected with edetates died from treatment—but mortality was not separately reported for each element. Graca et al. (1964) attributed the deaths to circulatory failure. In general, based on mortality data, the chloride compounds of rare earth elements were more toxic than the citrate or edetate compounds. During the first hour of treatment, samarium chloride produced 5−8% decreases in blood pressure, with ~12% decreases at the 100-minute and 18% decreases at the160-minute assessments. Graca et al. (1964) observed similar effects on blood pressure for samarium citrate during the first hour, but blood pressures at 100 and 160 minutes appeared to be similar to controls, based on a graph of outcomes. Samarium edetate did not affect blood pressure during the first 60 minutes of treatment, but it produced an approximate 20% decrease at 100 and 160 minutes. Injection of samarium chloride produced decreases in heart rate that progressed over time from approximately 10% at 30 minutes to approximately 75% at 160 minutes. Graca et al. (1964) observed minor variations in heart rate

among animals injected with samarium citrate and samarium edetate, although changes were generally ≤10%. Respiration rates were increased at all time points for all samarium compounds, with the most pronounced change observed in animals injected with samarium citrate (approximately 20 to 50%). Prothrombin time was markedly increased from approximately 5 to 10 seconds in controls to approximately 65 to >100 seconds for samarium chloride, 50 to 90 seconds for samarium citrate, and 45 to 75 seconds for samarium edetate. Coagulation times of approximately 10 minutes in controls increased to approximately 24 to 50 minutes for samarium chloride and approximately 18 to >100 minutes for samarium citrate. Graca et al. (1964) observed increased clotting times of ~30 minutes for samarium edetate only at the 160-minute observation point. Effects of samarium compounds on clotting parameters were generally consistent with the effects observed for other rare earths tested in the study—both in terms of the timing of effects and the relative toxicity of the three compounds tested. Gross and histopathological examinations revealed slight-to-moderate hyperemia of the lungs (data not reported) only in animals treated with chlorides of the rare-earth elements.

Lambert et al. (1990) administered samarium oxide 5.0 g/kg in water by gavage to 10 fasted Sprague-Dawley rats. No deaths or other clinical signs were observed in the 14-day observation period following dosing. Lambert et al. (1990) also observed no dermal irritation among six New Zealand Albino rabbits following application of 0.5-g samarium oxide to one intact and one abraded skin site that were occluded for 24 hours and observed for 72 hours. Lambert et al. (1990) observed minimal eye irritation among six New Zealand Albino rabbits treated with 0.1-g samarium oxide in the eye. Draize et al., 1944 scores were as follows:

- Three eyes rinsed with saline 30 seconds postinstallation: 5.3 at 24 hours; 3.3 at 48 hours; 0.7 at 72 hours.
- Three unrinsed eyes: 5.3 at 24 hours; 2.0 at 48 hours; 0 at 72 hours.

In Vitro Studies

Kostova and colleagues (2007, 2005) have demonstrated that certain complexes of samarium and other rare earth metals exhibit antineoplastic, antiproliferative, and other cytotoxic activity against tumor cells, in vitro. However, in vivo data were not available to develop dose-response relationships. In addition, these complexes were specially prepared for experimental medicinal testing and are unlikely to appear as site contaminants.

Toxicokinetics

Based on the available data for samarium and other light lanthanides, samarium is likely to be absorbed poorly from the gastrointestinal tract, deposited primarily in the liver and secondarily to bone, and excreted primarily in the feces. The limited oral acute lethality data suggest that gastrointestinal absorption of samarium and other rare earths is low. Comparison between available i.p. and oral LD_{50}s shows that the oral LD_{50}s exceed the corresponding i.p. LD_{50}s, which probably is due to the limited absorption of the ingested compounds. Wells and Wells (2001) noted that, in general, oral LD_{50}s for rare earth elements are about 10-fold higher than corresponding i.p. LD_{50}s, and Bruce et al. (1963) found i.v. administration also to be an order of magnitude more toxic than oral administration.

Toxicokinetics of Samarium and Compounds—Ulusoy and Whitley (2000) and Fairweather-Tait et al. (1997) investigated the use of rare earth elements as nonabsorbable fecal markers in humans. Ulusoy and Whitley (2000) orally administered a solution containing a

combination of five rare earth element oxides (samarium [1-mg Sm, 0.665 µmole], lanthanum [1-mg La; 7.2 µmole], terbium [7.5-mg Tb; 47.2 µmole], ytterbium [5-mg Yb; 28.9 µmole], and europium [10-mg Eu; 65.8 µmoles]) to six healthy subjects (five males and one female); seven healthy subjects (six males and one female) ingested a solution containing samarium oxide (1-mg Sm) and ^{57}Fe (2-mg Fe; compound not specified), which was included as a radioactive tracer to improve the accuracy of intake and excretion measurements. Fecal samples were collected for 1 week following ingestion of the test material. For subjects administered the solution containing the mixture of rare earth oxides, 94.3 ± 4.0% (mean ± SD) of the ingested samarium was recovered in feces. For subjects administered samarium oxide and ^{57}Fe, 103 ± 3.1% (mean ± SD) of the ingested samarium was recovered in feces. These results indicate that samarium oxide was very poorly absorbed (0−5.7%) following oral exposure. Similar results regarding the low oral absorption of the more soluble samarium chloride were reported by Fairweather-Tait et al. (1997), who administered diets containing samarium chloride (1-mg Sm) plus stable isotopes of iron (as $FeSO_4$) to healthy human subjects (3 males and 10 females). Total recovery of samarium in feces collected for 9 days postexposure was 103% (range of 96−106%), indicating that samarium chloride also was very poorly absorbed following oral administration. Studies evaluating the toxicokinetics of samarium following oral exposure in animals were not identified.

In an unpublished study aimed at developing a model for assessing lung deposition of promethium from analysis of excreta, Shipler et al. (1975) evaluated the toxicokinetics of inhalation exposure in 36 rats and 5 dogs exposed to a mixture of samarium oxide ($^{145}Sm_2O_3$) and promethium oxide ($^{143}Pm_2O_3$). Samarium was added to determine its usefulness as a carrier. Exposures were 30 minutes (nose only) for rats (strain and gender not reported) and 5 to 10 minutes (whole body) for dogs (breed and gender not reported). The concentrations of samarium and promethium in the aerosol were not reported. The ratio of ^{145}Sm to ^{143}Pm in the suspension used to generate the aerosol was about 3:1, and the total concentration of radioactivity in the aerosol was 0.0216 µCi/L for rats and ranged from 0.771 to 7.20 µCi/L for dogs. The mass median aerodynamic diameter (MMAD) of the aerosol was 3.4 µm for the study in rats and 2.3 µm for the study in dogs.

Shipler et al. (1975) sacrificed 12 of the 36 rats immediately after exposure for estimation of the lung burden of each element; remaining rats were sacrificed 14 and 30 days after exposure (12 rats at each sacrifice). Radioactivity in the lungs of dogs was measured 5 times during the 30-day postexposure period; dogs were sacrificed at the end of the 30-day period. Shipler et al. (1975) collected urine and feces from all animals throughout the 30-day postexposure period. Upon sacrifice, the following organs were analyzed for ^{145}Sm and ^{143}Pm: lungs, blood, liver, kidney, gastrointestinal tract, gonads, hepatic lymph nodes, tracheobronchial lymph nodes, heads, pelts, skeleton, and muscle. Among rats, data for ^{145}Sm in skeleton, kidney, and muscle were reported only for the 14-day postexposure assessment. Shipler et al. (1975) estimated the initial lung burden in rats immediately following exposure to be 1.05 µg Sm_2O_3; initial lung burden in dogs was estimated to range from 0.106 to 1.65 µg Sm_2O_3.

Shipler et al. (1975) reported that samples containing high concentrations of calcium and sodium salts might have considerable error in radioactivity counts. The distribution of both ^{145}Sm and ^{143}Pm in rats and dogs were very similar; representative results for ^{145}Sm are reported here. In rats sacrificed after 14 days, the skeleton, muscle, and kidneys were reported to contain 3.1%, 2.2%, and 0.27% (respectively) of the initial ^{145}Sm lung burden. In rat lungs, ^{145}Sm

content was 62% and 40% of the initial lung burden at 14 and 30 days postexposure, respectively. In rat livers, ^{145}Sm content was 2.9% and 4.0% of the initial lung burden on Postexposure Days 14 and 30, respectively. ^{145}Samarium was eliminated in feces and urine, with the highest amounts eliminated during the first two days following exposure. Shipler et al. (1975) reported fecal excretion during the first 2 days of exposure to be more than 3000% of the initial lung burden. That the fecal excretion of radioactivity far exceeded the calculated lung burden suggests that most of the aerosol was initially deposited to the nasopharynx and upper bronchial regions and cleared to the gastrointestinal tract, while much less was deposited in the pulmonary region. Urinary excretion during the first 2 days after exposure was 26.4% of the initial lung burden. Plots of both urinary and fecal excretion of radiation reveal a rapid initial phase over the first few days after exposure, with a slower second phase 10–30 days postexposure. Shipler et al. (1975) hypothesized that the results indicated two phases of clearance, the first associated with clearance of material via the gastrointestinal tract to the feces, and the second associated with clearance from more distal areas of the lung.

Shipler et al. (1975) sacrificed all dogs 30 days after exposure; the initial lung burden immediately following exposure was not determined. At the end of the 30-day postexposure period, ^{145}Sm was measured in several organs, including lungs, liver, kidneys, gastrointestinal tract, spleen, and skeleton; the content varied by individual dog but indicated the greatest distributions were to the liver and skeleton. Fecal excretion of ^{145}Sm 2 days after exposure ranged from 64% to 567% of the estimated initial lung burden, indicating substantial deposition in, or mechanical clearance to, the gastrointestinal tract. Shipler et al. (1975) reported urinary excretion data for only 1 dog, estimating that 0.3% of the initial lung burden was eliminated in the urine on Day 2; other time-points were not reported.

The results of these studies in rats and dogs (Shipler et al., 1975) indicate that aerosolized Sm_2O_3 and $^{143}Pm_2O_3$ were absorbed following inhalation exposure; however, due to substantial deposition of the material to the gastrointestinal tract, the relative contributions of pulmonary and gastrointestinal absorption to the overall absorption following inhalation exposure could not be determined.

Studies on the distribution and elimination of samarium compounds following parenteral exposure indicated that the liver, bones, and spleen were primary sites of initial distribution, and that samarium was eliminated in the urine and feces; however, distribution and elimination varied with the specific samarium compound (ICRP, 1981; Durbin et al., 1956; Rosoff et al., 1963). Durbin et al. (1956) investigated the distribution and elimination of oxides and chlorides of ^{153}Sm in groups of five female Sprague-Dawley rats following intramuscular injection of 0.3 or 0.6 µg of carrier compound[9] labeled with ^{153}Sm (30 or 75 µCi ^{153}Sm /rat); data were collected for 4 days. Distribution and elimination of radioisotopes of 14 other lanthanide oxides and chlorides also were investigated in the same study (Durbin et al., 1956). Approximately 30% and 50% of the injected ^{153}Sm was distributed to the bone and liver, respectively, and approximately 10% was excreted in urine and feces after 4 days (data presented graphically); the distribution of the remaining 15% of the administered dose was not reported. The initial distribution of samarium was similar to that observed for other light lanthanide elements (Durbin et al., 1956). Although long-term skeletal retention of ^{153}Sm was not evaluated in the

[9]The radioactive oxide was dissolved in 6N HCl, 10 mg of NaCl was added, then the solution was dried. Sodium citrate was then added and the pH was adjusted to neutral (presumably pH = 7 at 25C) with 9N NaOH.

study, skeletal retention curves for other light lanthanide elements (^{147}Pm and ^{144}Ce) showed two components, a labile component and a fixed component (Durbin et al., 1956). The labile component represented approximately 33% of the initial skeletal burden, with an elimination half-life of approximately 15 days; the stable component represented approximately 66% of the initial skeletal burden and appeared to be "fixed," with no apparent decrease in bone burden up to 256 days after administration. This corresponded to an elimination half-time exceeding 5 years. Data regarding the long-term effects of stored stable samarium were unavailable. However, it should be noted that such long-term deposition of radioactive samarium so close to the bone marrow—and its stem cells for RBCs and all white cell lines—could have serious health consequences.

Rosoff et al. (1963) evaluated the distribution and elimination of samarium chloride ($SmCl_3$), samarium nitriloacetate (SmNTA), and samarium edetate (SmEDTA) labeled with ^{153}Sm 24 hours after intravenous injection (0.051 mg Sm) into groups of 5 male CF1 mice. The cumulative 24-hour urinary excretion of ^{153}Sm was 58.7% of administered dose for SmEDTA; for SmNTA, and $SmCl_3$, was 12.4% and 3.3% of the administered ^{153}Sm dose, respectively. The 24-hour tissue distribution of ^{153}Sm was similar for $SmCl_3$ and SmNTA (data presented graphically), with the highest percentages of the administered ^{153}Sm distributed to liver (approximately 32% for $SmCl_3$ and 22% for SmNTA) and spleen (approximately 28% for $SmCl_3$ and 14% for SmNTA). Accumulation in bone was approximately 6% of administered ^{153}Sm for SmNTA and approximately 2% for $SmCl_3$. For SmEDTA, approximately 8% of the administered ^{153}Sm was distributed to bone, 4% to liver, and 1% to spleen.

Toxicokinetics of Rare Earths—Several reports have concluded that the toxicokinetics of light lanthanides (lanthanum, cerium, praseodymium, neodymium, promethium, and samarium) are similar (Haley, 1965; ICRP, 1981; Hirano and Suzuki, 1996; Mode, 1990; Wells and Wells, 2001); therefore, the toxicokinetic characteristics of other light lanthanide elements may apply to samarium.

The oral absorption of several lanthanide compounds, including samarium, lanthanum, terbium, ytterbium, and europium in humans was investigated in studies on their use as nonabsorbable fecal markers. Ulusoy and Whitley (2000) reported oral absorption of lanthanide oxides to range from 5.5 ± 4.5% (mean ± SD) for terbium to 6.5 ± 3.9% for ytterbium. Fairweather-Tait (1997) reported detecting no absorption of samarium chloride, with recovery of samarium in the feces exceeding 100% of the administered dose. These results indicate that lanthanide oxides and chlorides probably are poorly absorbed from the gastrointestinal tract.

Durbin et al. (1956) estimated that absorption of other lanthanide chloride and oxide compounds (^{144}Ce, ^{152,154}Eu, ^{160}Tb, and ^{170}Tm[10]), following oral exposure in rats, was <0.1% of the administered dose. Absorption of lanthanide elements following oral exposure is likely to vary with chemical form (e.g., soluble versus insoluble) and may be markedly enhanced by the presence of oxidizing agents, such as ferric iron, or under fasting conditions (Sullivan et al., 1986; Hirano and Suzuki, 1996). Samarium chloride ($SmCl_3$) is a relatively

[10]The primary decay modes for all of these isotopes involve β (including electron capture), γ, and X-ray emissions. These isotopes are not α-emitters (ICRP, 1983).

strong Lewis acid that forms insoluble hydroxides at neutral or alkaline pH; these reactions may limit the bioavailability of ingested samarium chloride relative to more water soluble samarium salts such as samarium nitrate.

As reviewed by Wells and Wells (2001), heavy lanthanides distribute primarily to the skeleton while the lighter lanthanides distributed primarily to the liver (45% and 65% of the administered doses for samarium and lanthanum, respectively). The skeleton is a secondary site of deposition for the light lanthanides. Excretion of the lanthanides occurs through the urine and feces in proportions that are dependent upon position of each element in the series. Light lanthanides such as samarium are excreted primarily in the feces; heavy lanthanides are excreted primarily in the urine, and the mid-series elements are excreted approximately equally.

Based on the available toxicokinetic data from animals and humans, Taylor and Legett (2003) published a biokinetic model to predict the disposition of lanthanide elements in humans. The model consists of compartments for soft tissue (including subcompartments for slow, intermediate, and rapid turnover), skeleton (six subcompartments for cortical and trabecular volume, surface and marrow), kidneys, urinary bladder, urine, blood, liver (three subcompartments), gastrointestinal tract, gonads, and feces. Based on the available information, Taylor and Legett (2003) concluded that elements within the lanthanide series could be divided into five groups, based on neighboring elements having similar properties, and derived set-specific parameters for each group on the basis of existing data for rats, humans, and dogs. In their model, neodymium, promethium, and samarium were treated as a similar group with common parameters.

Taylor and Legett (2003) compared predictions from their generic model with existing human data and existing International Commission on Radiological Protection (ICRP) models for radioactive promethium and gadolinium. Good agreement between the generic model and the ICRP models for radioactive promethium and gadolinium was observed for whole-body retention, urinary and fecal excretion, and absorbed doses to the bone surfaces, bone marrow, and liver. However, the doses predicted for the kidneys and testes were three orders of magnitude higher than those estimated by existing ICRP models. In summary, Taylor and Legett (2003) concluded that their model appeared to be adequate for use in general radiological protection, but should be applied with appropriate caution for interpretation of data from bioassays.

Genotoxicity

There is limited in vitro evidence that stable nonradioactive rare earth metals have genotoxic activity (Jha and Singh, 1995; Hui et al., 1998). However, no data specific to samarium were identified.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfDs FOR SAMARIUM COMPOUNDS

Data on the oral toxicity of subchronic or chronic human exposure to stable samarium compounds have not been identified. Six animal studies were identified that might have assisted in development of provisional subchronic RfDs for samarium compounds. However, only two

of the studies (Haley et al., 1961; Weilin et al., 2006) provide information that can be considered for quantitative derivation of p-RfDs. Hutcheson et al. (1975) provides quantitative data—but only for mixtures of lanthanides. Bruce et al. (1963) provides information on the relative toxicity of samarium compounds, while two Chinese studies of reproductive factors (Chen et al., 2005; Hu et al., 2007) were available only as abstracts that provided insufficient information.

Information on the toxicity in experimental animals of repeated oral exposures to samarium compounds alone (i.e., not as part of a mixture with other lanthanide compounds) was limited to a 12-week dietary study of samarium chloride in rats (Haley et al., 1961) and a 5-month drinking water study in rats (Weilin et al., 2006). Haley (1961) reported no effects on the parameters evaluated (body weight, hematology, and histopathology of selected tissues) following dietary treatment with samarium chloride; thus, the highest doses tested (908-mg $SmCl_3$/kg-day or 532-mg Sm/kg-day in males; 1001-mg $SmCl_3$/kg-day or 586-mg Sm/kg-day in females) were identified as freestanding NOAELs. In the absence of other data, this NOAEL provides a point of departure (POD) from which to derive a p-RfD for samarium chloride. This POD is supported by the observation that, even acutely, samarium chloride does not seem to be toxic by the oral route and various lines of evidence suggest limited oral absorption.

The potential for reproductive or developmental effects of oral exposure to stable samarium was investigated in a 3-generation feeding study on a mixture of lanthanide oxides (oxides of lanthanum, samarium, europium, terbium, dysprosium, thulium, and ytterbium) and other metals (scandium oxide, chromium oxide, and barium sulfate) in mice (Hutcheson et al., 1975). Results showed no effects on reproduction, development, growth, adult body weight, or other parameters, including hematology, serum proteins, and gross pathology, yielding a freestanding NOAEL of 69 mg /kg-day for the mixture of lanthanide oxides. Data from this study are not useful for assessing samarium toxicity, given the coexposure to multiple lanthanides and the failure to identify a toxic endpoint.

Data cited in this document strongly suggest that different chemical forms of samarium have different toxic potencies. However, because repeated oral dose studies were identified only for samarium chloride and samarium nitrate, data with which to compare the subchronic or chronic oral toxicities of other samarium compounds were not available. The only other data available on the oral toxicity of samarium alone were an acute oral LD_{50} of 901-mg Sm/kg for samarium nitrate in female rats (Bruce et al., 1963) and an acute oral lethality study on samarium chloride in mice that observed no mortalities at 1172-mg Sm/kg, the highest dose tested (Haley et al., 1961). Due to the limited information available, it is not possible to determine if the differences in oral acute lethality and subchronic toxicity for the chloride and nitrate compounds reflected differences in toxicokinetics of the samarium compounds. Differences in acute lethality might also have been attributable to the animal species tested (mice vs. rats), gender differences, or other differences in experimental methods (see discussion under Acute Toxicity).

Weilin et al. (2006) reported increased relative pancreas and lung weights and increased liver MDA concentrations among male and female SD rats treated with samarium nitrate in drinking water at the lowest dose (0.438-mg $[SmNO_3]_3$/kg-day or 0.196-mg Sm/kg-day). This LOAEL provides a POD from which derivation of a p-RfD for samarium nitrate was considered. Data for relative pancreas and lung weight were modeled using U.S. EPA (2000) benchmark

dose modeling software. However, none of the models provided adequate fit to the data, even when the highest dose data were dropped and when nonhomogeneous models were used. Application of the LOAEL of 0.438-mg $(SmNO_3)_3$/kg-day or 0.196-mg Sm/kg-day as the POD introduce an unacceptable level of uncertainty, so a p-RfD for samarium nitrate was not derived. However, the Appendix of this document contains a screening value for samarium nitrate that may be useful in certain instances. Please see Appendix A for details.

The Haley et al. (1961) 12-week oral toxicity study of samarium chloride in rats serves as the critical study for derivation of the subchronic p-RfD for the chloride salt. The freestanding NOAEL of 908-mg $SmCl_3$/kg-day or 532-mg Sm/kg-day in male rats was used to derive a **subchronic p-RfD for samarium chloride** as follows:

$SmCl_3$ Subchronic p-RfD = NOAEL ÷ UF
= 908 mg Sm Cl_3/kg-day ÷ 1000
= **0.9 or 9×10^{-1} mg $SmCl_3$/kg-day**

$SmCl_3$ Subchronic p-RfD as Sm = 532 mg Sm/kg-day ÷ 1000
= **0.5 or 5×10^{-1} mg Sm/kg-day**

The composite UF of 1000 is composed of the following:

- A UF_A of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF_D of 10 is applied for uncertainty in the database. The critical study used only six animals per dose group and reproductive data were available only as abstracts of Chinese studies (Hu et al., 2007; Chen et al., 2005). Hutcheson et al. (1975) demonstrated a freestanding NOAEL of 69 mg/kg-day for reproductive and developmental endpoints following oral exposure to a mixture of lanthanide oxides, suggesting that the p-RfD derived for samarium chloride might be protective for potential reproductive endpoints. However, the relative toxicities of the oxides and chlorides of samarium could not be determined.

Given the uncertainty in relative potencies of samarium compounds, **this subchronic p-RfD should be applied only to samarium chloride**.

Confidence in the principal study (Haley et al., 1961) is low. Although both genders were tested in this study, only six animals per gender were used for each dose group, resulting in the possibility that responses of ~10% or more likely would be missed. The toxicological evaluation in this study was limited to body-weight measures, selected hematological parameters, and histopathology of a subset of organs. Neither serum chemistry nor urinalysis endpoints were evaluated, nor were organ weight measurements provided. A LOAEL was not identified. Confidence in the database on samarium is low. Apart from the critical study, the only other oral toxicity studies conducted on samarium chloride alone were acute lethality studies in rats and mice. Oral absorption of samarium chloride is estimated to approach zero, based on various lines of evidence discussed in this document. There were no data to indicate

the toxicological endpoint(s) or target organ(s) of oral exposure to stable samarium chloride. A reproduction and developmental study on a mixture of lanthanide oxides indicated that the mixture did not adversely affect reproduction or development; however, no studies of the reproductive or developmental effects of stable samarium chloride alone were available. Low confidence in the subchronic p-RfD results.

The limited available data did not provide assurance that a p-RfD based on data for either samarium chloride or samarium nitrate would be adequate for other samarium compounds. The Weilin et al. (2006) subchronic toxicity data for samarium nitrate suggest a LOAEL POD more than 2000 times lower than the NOAEL POD for samarium chloride. The apparent proximity of the acute oral LD_{50} of 901-mg Sm/kg for samarium nitrate in female rats (Bruce et al., 1963) and the subchronic NOAEL of 586-mg Sm/kg-day for samarium chloride in female rats (Haley et al., 1961) also suggests a difference in toxicity between compounds. In the absence of evidence explaining the large differences in apparent toxicity between the chloride and nitrate salts, the p-RfD for samarium chloride should be used with caution. The large differences in acute and subchronic toxicity, discussed above, preclude generalization of the p-RfD for samarium chloride to other samarium compounds.

A chronic p-RfD is not derived for any samarium compound. There were no chronic exposure studies in any species. The uncertainties about the subchronic POD from the Haley et al. (1961) samarium chloride feeding study preclude its extrapolation to chronic exposures. Toxicokinetic studies of lanthanide elements indicated that light lanthanides are deposited primarily in the liver and spleen, and secondarily in the skeleton. In their review, Wells and Wells (2001) noted that rare earth chlorides in the liver and spleen are not readily excreted. In addition, a portion of the skeletal burden of light lanthanides has exhibited extremely slow retention kinetics (e.g., half-time exceeding 5 years in rats; Durbin et al., 1956). Although long-term skeletal retention of samarium has not been evaluated, the potential for prolonged retention of samarium in the body increases the uncertainty in extrapolating from subchronic data to estimate effects of chronic exposure. As a consequence of the uncertainty regarding long-term retention in the body and other uncertainties regarding the data that are described above, no chronic p-RfD is derived for any samarium compound.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfCs FOR SAMARIUM

Studies investigating the effects of inhalation exposure of humans and animals are limited to evaluations on mixtures of rare earth metals containing samarium. Evidence for point-of-entry effects (pulmonary lesions) associated with inhalation of mixtures of rare earth metals (Schepers, 1955a,b; Schepers et al., 1955) indicated that route-to-route extrapolation from oral data would not be appropriate. The lack of suitable data precludes derivation of subchronic and chronic p-RfCs for samarium.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR SAMARIUM

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to samarium in humans or animals have not been located in the available literature. Haley et al. (1961) reported that no histological changes were found in rats orally exposed to samarium chloride for 90 days, but this study does not support a carcinogenicity assessment due to insufficient duration of exposure and lack of a posttreatment observation period. Studies on the genotoxicity or mutagenicity of stable samarium compounds have not been located. In accordance with the 2005 *Guidelines for Cancer Risk Assessment* (U.S. EPA, 2005) for chemicals with inadequate human and animal data, this review concludes that data for stable (nonradioactive) samarium compounds provided "Inadequate Information to Assess [the] Carcinogenic Potential" of samarium or its compounds.

Quantitative Estimates of Carcinogenic Risk

The lack of carcinogenicity data precludes derivation of quantitative estimates of cancer risk for nonradioactive samarium compounds.

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APPENDIX A. DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfDs FOR SAMARIUM COMPOUNDS

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for samarium. However, information is available for this chemical, which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Weilin et al. (2006) reported increased relative pancreas and lung weights and increased liver MDA concentrations among male and female SD rats treated for 5 months with samarium nitrate in drinking water at the lowest dose (0.438 mg $[SmNO_3]_3$/kg-day or 0.196 mg Sm/kg-day). This LOAEL provides a POD from which a screening RfD for samarium nitrate can be derived. Data for relative pancreas and lung weight were modeled using U.S. EPA (2000) benchmark dose modeling software. However, none of the models provide adequate fit to the data—even when the highest dose data were dropped and when nonhomogeneous models were attempted. Consequently, the LOAEL of 0.438 mg $(SmNO_3)_3$/kg-day or 0.196 mg Sm/kg-day is used as the POD to derive a **screening subchronic p-RfD** as follows:

$Sm(NO_3)_3$ Screening Subchronic p-RfD = LOAEL ÷ UF
= 0.438 mg $(SmNO_3)_3$/kg-day/10,000
= 0.0000438 mg $(SmNO_3)_3$/kg-day
= **4×10^{-5} mg $(SmNO_3)_3$/kg-day**

OR

$Sm(NO_3)_3$ Screening Subchronic p-RfD as Sm = 0.196 mg Sm/kg-day/10,000
= 0.0000196 mg Sm/kg-day
= **2×10^{-5} mg Sm/kg-day**

The composite UF of 10,000 is made up of the following uncertainty factors:

- A UF_A of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.
- A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.
- A UF_L of 10 is applied for use of a LOAEL POD.

- A UF_D of 10 is applied for uncertainty in the database. The critical study used only six animals per dose group and reproductive data were available only as abstracts of Chinese studies (Hu et al., 2007; Chen et al., 2005). Hutcheson et al. (1975) demonstrated a freestanding NOAEL of 69 mg/kg-day for reproductive and developmental endpoints following oral exposure to a mixture of lanthanide oxides, which suggests that the p-RfD derived for samarium chloride might be protective for potential reproductive endpoints. However, the relative toxicities of the oxides and chlorides of samarium could not be determined.