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Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Neodymium Chloride
(CASRN 10024-93-8)

Superfund Health Risk Technical Support Center
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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) NEODYMIUM CHLORIDE (CASRN 10024-93-8)

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

Neodymium (Nd; CASRN 7440-00-8) is a rare earth element belonging to the lanthanide[1] series of the periodic table. Neodymium compounds are used in carbon-arc lamps for movie projection, permanent magnets, organic reagents, lasers, and alloys. Neodymium can form water-soluble compounds (e.g., neodymium chloride and neodymium nitrate) and insoluble compounds (e.g., neodymium oxide and neodymium hydroxide). Water-soluble neodymium compounds (e.g., neodymium 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 (nonradioactive) forms of neodymium and its compounds, and derives a toxicity value only for neodymium chloride. Neodymium chloride typically is found as the hexahydrate (CASRN 13477-89-9).

No RfD, RfC, or carcinogenicity assessment for stable, nonradioactive neodymium or neodymium compounds is available on IRIS (U.S. EPA, 2009). Subchronic or chronic RfDs or RfCs for neodymium 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) has not produced a Toxicological Profile for neodymium, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2009). The chronic toxicity and carcinogenicity of neodymium have not been assessed by the International Agency for Research on Cancer (IARC, 2009) or the National Toxicology Program (NTP, 2005, 2009). The American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the Occupational Safety and Health Administration (OSHA, 2009), and the National Institute of Occupational Safety and Health (NIOSH, 2005) have not established occupational exposure standards for neodymium. A toxicological review of the lanthanides is identified that derived toxicity values for several lanthanides—but not for neodymium or its compounds (TERA, 1999).

[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).

Literature searches were conducted from the 1960s through December 2007 for studies relevant to the derivation of provisional toxicity values for neodymium. Databases searched include MEDLINE, TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. Reviews of rare earth or lanthanide toxicity (Haley, 1991; TERA, 1999; Wells and Wells, 2001) also have been consulted for pertinent information, and the literature search was updated in July 2009.

REVIEW OF PERTINENT LITERATURE

Overview of Rare Earth Chemical Properties

Environmental and occupational exposure to neodymium 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) have 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); neodymium 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).

[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.

Human Exposure to Neodymium and Compounds

The anticoagulant properties of the rare earth metals were studied in the early years of the twentieth century; investigators were interested in using rare earth metals to treat phlebitis. These studies involved in vitro measurements of clotting time and in vivo studies using intravenous administration of various rare earth metal salts in dogs, rabbits, and human volunteers. None of these studies used oral or inhalation exposure and, as such, do not support derivation of a subchronic or chronic p-RfD or p-RfC. Studies conducted by Beaser et al. (1942) are representative of this genre. Beaser et al. (1942) injected human volunteers intravenously (various experiments and protocols; injections were either administered one time or were repeated with inconsistently varied doses for up to 17 daily injections) with salts of neodymium including neodymium nitrate, neodymium lactate and neodymium acetate, at doses ranging from 3−18 mg salt/kg body weight, and measured blood clotting time thereafter for up to several weeks. The precise protocol varied with each patient due to the exploratory nature of the study, and the reporting of the methods and results was not always explicit. All salts increased clotting time (normally about 15 minutes) 2−4 times above normal, peaking at about 1 hour after injection. Beaser et al. (1942) considered the minimum effective dose to be 5−8 mg/kg body weight and noted the peak increase to occur within 1 hour of exposure, then to decline. Beaser et al. (1942) noted that successive injections of small doses could prevent the decline in clotting time and that doses >14 mg salt/kg body weight (specific salts not specified other than previous note that nitrates, acetates and lactates were used) rendered the blood "uncoagulable." Adverse side effects—including fever, chills, muscle aches, abdominal cramps, hemoglobinemia and hemoglobinuria—were noted in the volunteers and, as such, further experimentation with rare earth metals as an anticoagulant therapy was discontinued.

Human Exposure to Rare Earth Mixtures

Human toxicity data relevant to environmental exposures to neodymium were limited to case reports of pneumoconiosis and progressive pulmonary fibrosis in workers exposed to 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 reports 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).

The case reports generally detailed the pulmonary findings of individuals, so there is 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 are also 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 exposure to rare earth elements and pneumoconiosis or fibrosis, the relative contribution of neodymium (or any other individual element) to the development of pneumoconiosis has not been established. Furthermore, the available human case studies do not contain dose-response information that could be used to develop provisional toxicity values for any of the stable nonradioactive lanthanides.

Animal Studies

Oral Exposure—Neodymium and Compounds

Only one repeated dose oral study of neodymium alone (without other rare earth compounds) has been identified in the literature search. Groups of six male and six female CRW rats were fed 0, 0.01, 0.1, or 1% dietary neodymium chloride (purity not reported) for 90 days (Haley et al., 1964). Compound intake is estimated to be 8.4, 84, or 840 mg $NdCl_3$/kg-day (4.8, 48, or 483 mg Nd/kg-day) in the males and 9.5, 95, or 950 mg $NdCl_3$/kg-day (5.5, 55, or 547 mg Nd/kg-day) in the females. These doses[6] have been calculated using the average body weights of 310 g for males and 210 g for females (data estimated from growth curves) and default food consumption rates for rats of 0.026 kg/day for males and 0.020 kg/day for females (U.S. EPA, 1988). Body weight and hematology (total erythrocytes, total leucocytes, differential cell count, platelets, hemoglobin, and hematocrit) were measured biweekly, and histological examinations (heart, lung, liver, kidney, pancreas, spleen, adrenal, and small intestine) were performed at the end of the study. No exposure-related histopathological or other changes were observed in either gender, yielding a freestanding NOAEL of 840 mg $NdCl_3$/kg-day in males and 950 mg $NdCl_3$/kg-day in females.

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 in order 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)

[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).
[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.

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[7] with an error of 5%. Table 1 shows 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 1. 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.

Hutcheson et al. (1975) reported neither dose nor food intake during the study. Therefore, daily doses of 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 the U.S. EPA (1988) allometric equation relating food consumption (kg food/day) to body weight (kg) for laboratory mammals. Table 2 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 5 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).

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

Table 2. 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 3 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 they were 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.

Hutcheson et al. (1975) 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. (1975) 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). This study is not useful for assessing neodymium toxicity, as neodymium was not one of the rare earth elements included in the mixture.

Table 3. 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 $p = 0.69$.

Inhalation Exposure—Neodymium and Compounds

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

A study using intratracheal instillation of neodymium oxide (Mogilevskaya and Raikhlin, 1967) demonstrated the development of emphysema and limited development of fibrosis in rats. An unspecified number of rats (strain, gender, age, weight not reported) were exposed to neodymium oxide (as 50 mg dust suspended in 0.6% saline) by a single intratracheal instillation. A group of eight unexposed rats served as controls. Rats were weighed monthly and killed 8 months after exposure. The heart, lungs, and livers were weighed and ratios of organ weight to body weight were determined. Internal organs (not specified) were examined histologically. Rats given the dust weighed 17% less than controls at the end of the study (262 ± 18.2 g vs. 317 ± 18.33 g for controls). Absolute organ weights were not presented; the ratios of heart-to-body-weight and liver-to-body-weight were comparable between exposed and control rats. The group mean ratio of lung-to-body weight appears to be elevated in exposed rats (1.27, standard deviation, number of animals not reported) in comparison with controls (0.92, $n = 8$, standard deviation not reported), and study authors reported the increase to be statistically significant. Macroscopic evidence of emphysema was noted. Microscopic examination revealed the formation of granulomata consisting of giant multinucleate cells containing dust particles, lymphoid cells, fibroblasts, and histocytes. The granulomata varied in size and were found around the pulmonary vessels and bronchi and in the interlobular connective tissue and alveolar septa. Mogilevskaya and Raikhlin (1967) reported that there was very slight formation of connective tissue fibers (short, thin collagen fibers within the cells in the granulomata) in comparison with that seen (greater extent) following a similar experiment conducted with yttrium oxide. There were no changes in pulmonary tissue beyond the areas of dust accumulation, no neoplastic changes, and no histological changes in unspecified "other internal organs." This study is of limited utility for toxicity assessment, as data collected after

intratracheal instillation of neodymium are of uncertain relevance to environmental exposure pathways (oral, inhalation).

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 (whole body) study in guinea pigs exposed to mixtures containing several (insoluble) rare earth elements, 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, for 3 years. Schepers (1955a,b) and Schepers et al. (1955) did not report the concentrations of neodymium 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 et al. (1955a) 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 et al. (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 et al. (1987), other factors that may explain the differences in human and animal findings

include chemical type, physiochemical form, dose, and duration of exposure. In any case, the relevance of studies by Schepers (1955a,b; Schepers et al., 1955) to neodymium toxicity is uncertain due to the lack of information exposure concentrations and the neodymium content of the mixtures.

Other Studies

Acute Exposure

Acute Lethality Studies—Acute oral lethality studies have been conducted for neodymium chloride and neodymium nitrate (see Table 4). Haley et al. (1964) reported an oral LD_{50} of 3024 mg Nd/kg for neodymium chloride[8] (specific details regarding administration of test substances were not reported) in male CF1 mice (neither age nor weight were reported). Mice were observed for 7 days following dosing. Haley et al. (1964) reported clinical signs of toxicity (including ataxia, writhing, labored respiration, walking on toes with arched back, and sedation) following either oral exposure or intraperitoneal injection with neodymium chloride or praseodymium chloride. No further details were provided, and no other information on the potential neurotoxicity of neodymium or other rare earth metals was identified in the literature search or reviews. Bruce et al. (1963) reported a lower oral LD_{50} of 905 mg Nd/kg for neodymium nitrate, administered by stomach tube in 50% aqueous solution, in female Sprague-Dawley rats (adults, 190−250 g) observed for 30 days following dosing.

Intraperitoneal acute lethality studies have been conducted for neodymium chloride, nitrate, citrate, and edetate compounds (see Table 4), resulting in LD_{50}s that often varied by compound and species. For neodymium chloride, Graca et al. (1957) reported an i.p. LD_{50} of 81 mg Nd/kg in guinea pigs (300−500grams; age, gender and strain not reported) while Haley et al. (1964) reported an i.p. LD_{50} of 346 mg Nd/kg in male CF1 mice. Graca et al. (1957, 1962) noted precipitate at the injection site of animals receiving intraperitoneal injections of neodymium chloride, indicating that absorption was incomplete and noting that the inflammatory response associated with the precipitate might complicate the interpretation of toxicity. For neodymium nitrate, Bruce et al. (1963) reported identical i.p. LD_{50}s in female Sprague-Dawley rats and female CF1 mice (89 mg Nd/kg).

Graca et al. (1962) tested the acute i.p. lethality of neodymium in citrate and edetate complexes in mice and guinea pigs. The test materials were described as "chloride-citrate" and edetate complexes or chelates; however, the exact nature and molecular formulas or weights 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 units of mg $NdCl_3$/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 $NdCl_3$ equivalents, or if all of the test materials were complexes of neodymium chloride. As a consequence of this uncertainty, the LD_{50}s reported by Graca et al. (1957, 1962) cannot be considered reliable indicators of the acute i.p. toxicity of the citrate and edetate compounds. Graca et al. (1957, 1962) reported i.p. LD_{50}s for neodymium citrate ranging from 138.0 to 140.0 mg $NdCl_3$/kg in CFW albino mice (age and gender not reported) and from 40.5 to 52.86 mg $NdCl_3$/kg in guinea pigs (age, strain and gender not reported) while i.p. LD_{50}s for neodymium edetate were 126.24 mg $NdCl_3$/kg in CFW albino mice and 142.33 mg $NdCl_3$/kg in

[8]Based on an LD_{50} of 5250 mg $NdCl_3$/kg: the ratio of Nd to Cl on the basis of molecular weight is 0.576; 0.576 × 5250 mg $NdCl_3$ = 3024 mg Nd/kg. Similar conversions are used to convert values for other salts, etc. to mg Nd/kg.

guinea pigs (Graca et al, 1962). These LD_{50}s should be interpreted cautiously, given the uncertainties outlined above.

TABLE 4. ACUTE LETHALITY OF STABLE NEODYMIUM COMPOUNDS FOLLOWING ORAL AND PARENTERAL EXPOSURE

COMPOUND	SPECIES/STRAIN (GENDER)	ROUTE OF EXPOSURE	LD_{50} IN MG ND/KG BODY WEIGHT[A]	REFERENCE
Neodymium chloride	Mice/CF1 (male)	oral (not specified)	3024 (2724−3358)	Haley et al. (1964)
	Mice/CF1 (male)	i.p.	346 (324−369)	Haley et al. (1964)
	Mice/CFW albino (NR)	i.p.	201 (171−235)[b] 200[b]	Graca et al. (1957) Graca et al. (1962)
	Guinea pigs (gender, strain: NR)	i.p.	81 (57−113)[b] 85[b]	Graca et al. (1957) Graca et al. (1962)
Neodymium nitrate	Rats/Sprague Dawley (female)	oral (gavage, 50% aqueous solution)	905 (624−1312)	Bruce et al. (1963)
	Mice/CF1 (female)	i.p.	89 (73−108)	Bruce et al. (1963)
	Rats/Sprague Dawley (female)	i.p.	89 (76−104)	Bruce et al. (1963)
	Rats/Sprague Dawley (female)	i.v.	3.0 (2.3−4.0)	Bruce et al. (1963)
	Rats/Sprague Dawley (male)	i.v.	22 (18−28)	Bruce et al. (1963)

[a](): 95% confidence limits, as reported by study authors.
[b]Precipitate observed at injection site; inflammatory response associated with precipitate confounds interpretation of toxicity associated with the chemical itself.
NR: not reported.
i.p.: intraperitoneal injection.
i.v.: intravenous injection.

Bruce et al. (1963) reported intravenous LD_{50}s of 22 and 3.0 mg Nd/kg in male and female Sprague-Dawley rats, respectively, for neodymium nitrate, indicating that female Sprague-Dawley rats may be more sensitive than males. Parallel results (i.e., lower i.v. LD_{50}s for females than for males) for nitrates of neodymium, cerium, and praseodymium in the same study support the gender difference. 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 neodymium compounds. As noted earlier, the available LD_{50}s for edetate and citrate forms of neodymium (Graca et al., 1957, 1962) cannot be considered reliable due to uncertainty in the reported doses. The intravenous lethality data are also 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 neodymium chloride in mice and guinea pigs and neodymium nitrate in mice and rats suggest that the acute i.p. toxicity of these neodymium compounds is of comparable order of magnitude; LD_{50}s ranged between 89 and 346 mg Nd/kg. It should be noted that the one mouse i.p. LD_{50} for neodymium nitrate is for female mice (Bruce et al., 1963), while the LD_{50}s for neodymium chloride are for male mice (Haley et al., 1964) or for mice of unspecified gender (Graca et al., 1957, 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 neodymium chloride (Graca et al., 1957, 1962), the absorption of neodymium chloride may have been affected by the formation of insoluble hydroxides or protein complexes at the injection site.

The oral acute toxicity data for neodymium chloride and neodymium nitrate are not comparable, primarily because the studies were conducted in different species, and the available data do not rule out species differences in absorption or toxicity. 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 neodymium 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 neodymium 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 neodymium.

Data on the acute oral or parenteral toxicity of insoluble neodymium 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 toxicity 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—Beaser et al. (1942) injected rabbits (gender, strain, age body weight not reported) with neodymium nitrate at doses of 10, 20, 30, and 60 mg/kg body weight and measured clotting time for 5 hours after injection[9]. No effect was observed at 10 mg salt/kg. Clotting times were increased to >120 minutes at the higher doses approximately 1 hour after injection. Clotting times dropped dramatically between the first and second hours of exposure, and did not return to normal with the formation of a true clot for days after exposure.

[9]This experiment is one of many carried out by these investigators and simultaneously reported; neither the methods nor the results are reported clearly.

Beaser et al. (1942) reported that phlebitis was observed at the site of injection within 24 hours of administration, and that edema and necrosis occurred subsequently.

Graca et al. (1964) investigated the effects of acute i.v. exposure to rare-earth element compounds (chlorides, citrates and edetates) on heart rate, blood pressure, respiration, and clinical hematology in anaesthetized male and female dogs (breed, number, and gender not specified). Aqueous solutions of 15 rare earth elements, equivalent to 5% of the chloride, were injected into a cannula inserted into the left femoral vein. There were 10 doses of 10 mg/kg each (as the chloride or its equivalent in the chelates) that were injected at 10-minute intervals. For each element, nine dogs were divided into groups of three, each treated with the chloride, citrate or edentate; three groups of control dogs were injected with sodium citrate (n = 6), ammonium 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 liver, spleen, kidney, lung, sternum, mesentery lymph nodes, heart, adrenal, and ovaries or testes tissues were collected for histopathology. 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 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 were 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, the lanthanide chloride compounds as a group were more lethal than the citrate or edetate compounds. Neodymium chloride produced a ~15% decrease in blood pressure 1 hour after treatment, with a ~30% decrease at 100 minutes and ~20% at 160 minutes after treatment. Neodymium edetate had little effect on blood pressure, with a maximal decrease of 12% after 100 minutes and less than 5% by 160 minutes. The effect of neodymium citrate on blood pressure was more rapid; blood pressure decreased by ~12% at 10 minutes and by ~30% at 30 minutes, then declined to 10−18% between 100 and 160 minutes. Injection of neodymium chloride produced decreases in heart rate that progressed over time by ~5% at 10 minutes to ~20−25% at ≥100 minutes. Graca et al. (1964) observed a similar pattern, with smaller decreases in heart rate, for both the citrate and edetate compounds. Respiration rate was increased at all time points for all neodymium compounds, with the most pronounced change observed in animals treated with neodymium citrate (approximately 40 to 30% at the 100- and 160-minute observation times, respectively). Prothrombin times measured at the 30−160-minute assessment points were markedly increased from approximately 5−10 seconds in controls to >100 seconds for all three compounds at the 60-, 100-, and 160-minute measurement intervals. Neodymium chloride and neodymium citrate also had prothrombin times >100 seconds at the 30-minute timepoint. Only neodymium chloride had a markedly increased prothrombin time (55 seconds) at the 10-minute timepoint. With respect to coagulation times, neodymium edetate had little effect over the 160 minutes of testing. Compared to controls (coagulation times of approximately 10 minutes), coagulation times were increased to >60 minutes for neodymium chloride and neodymium citrate at all time points from 30 minutes onward (30, 60, 100, 160 minutes). Graca et al. (1964) observed effects on clotting time for neodymium edetate only at the 160-minute observation point (~18 minutes). The observed effects on clotting variables

for neodymium chloride were consistent with the effects observed for other lanthanides 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.

The testicular calcium concentration was increased more than 2-fold higher than that of controls in ddY mice (body weight = 25−30 grams) given a single i.v. injection of neodymium chloride (either 20 or 200 µmoles neodymium chloride/kg; equivalent to 5 and 50 mg neodymium chloride/kg, respectively[10]) and assessed 5 days later (Nagano et al., 2000). No effects on testicular weight or lipid peroxidation were reported. The relevance of the observed increase in testicular calcium to toxicity is unknown.

Kostova and colleagues (2008, 2005, 2004) have demonstrated that certain complexes of neodymium 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 other light lanthanides, neodymium 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 neodymium 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. Toxicokinetic information on neodymium and compounds, and rare earths in general, are discussed in the sections below.

Toxicokinetics of Neodymium and Compounds—Studies evaluating the toxicokinetics of oral or inhaled neodymium in humans or animals have not been identified. Durbin et al. (1956) investigated the distribution and elimination of ^{147}Nd in groups of five female Sprague-Dawley rats following intramuscular injection of 2.3−4.6 µCi of ^{147}Nd-labeled neodymium oxide (dose not reported; in 1.1−3.7 µg of a carrier[11]). Distribution and elimination of radioisotopes of 14 other lanthanide elements also investigated in the same study. Urine and feces were collected for 4 days after administration; selected tissues were analyzed for ^{147}Nd upon sacrifice 4 days after dosing. Approximately 30% and 40% of the administered ^{147}Nd was distributed to the bone and liver, respectively, and approximately 18% was excreted in urine and feces after 4 days (data presented graphically); the distribution of the remaining 12% of the administered dose was presumed by the study authors to be in the remaining animal tissues. The initial distribution of neodymium was similar to that observed for other light lanthanide elements (Durbin et al., 1956). Although long-term skeletal retention of ^{147}Nd was not evaluated in the study, skeletal retention curves for other light lanthanide elements (^{147}Pm and ^{144}Ce) showed two

[10]e.g., 250.599 g/mole × 20 µmole × 1 × 10^{-6} mole/µmole = 0.005 g/mole or 5 mg/mole.
[11]10 mg of NaCL was added to the radioactive oxide originally dissolved in 6N HCl, then dried. Sodium citrate was then added and the pH was adjusted to neutral (presumably pH = 7 at 25°C) with 9N NaOH.

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 fixed component represented approximately 66% of the initial skeletal burden, 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 neodymium were unavailable. However, it should be noted that such long-term deposition of radioactive neodymium so close to the bone-marrow—and its stem cells for RBCs and all white cell lines—could have serious health consequences.

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 neodymium.

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 experimental animal absorption of chlorides and oxides of ^{144}Ce, $^{152,154}Eu$, ^{160}Tb, and ^{170}Tm following oral exposure was <0.1% of the administered dose; oral absorption of neodymium chlorides and oxides seem likely to be in the same range. Absorption of lanthanides 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). Neodymium chloride ($NdCl_3$) is a relatively strong Lewis acid that forms insoluble hydroxides at neutral or alkaline pH; these reactions may limit the bioavailability of ingested neodymium chloride relative to more water soluble neodymium salts such as neodymium nitrate. Following intramuscular injection, absorption of lanthanides from the injection site was substantially complete (<6.5% not absorbed) within 4 days (Wells and Wells, 2001).

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.

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 dose 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 neodymium, are excreted primarily in the feces; heavy lanthanides are excreted primarily in the urine, and the midseries elements are excreted approximately equally.

Based on the available toxicokinetic data from animals and humans, Taylor and Leggett (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 Leggett (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 Leggett (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 kidney and testes were three orders of magnitude higher than those estimated by existing ICRP models. In summary, Taylor and Leggett (2003) concluded that their model appeared to be adequate for use in general radiological protection, and could be applied with appropriate caution for the interpretation of data from bioassays.

Genotoxicity

There is limited evidence that stable nonradioactive neodymium has genotoxic activity. Nonradioactive neodymium oxide induced a dose-related increase in the frequency of chromosomal aberrations in bone marrow cells of Swiss mice that were treated with single intraperitoneal doses of 5.30−43.00 mg/100g, equivalent to 4.54−36.87 mg Nd/kg (Jha and Singh, 1995). The maximum number of chromosomal aberrations per cell relative to negative controls (approximately 7 times higher) was observed in cells harvested 6 hours postexposure.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfDs FOR NEODYMIUM CHLORIDE

Data on the oral toxicity of subchronic or chronic exposure of humans to stable neodymium compounds have not been identified. Three animal studies were identified that have the potential to inform derivation of provisional subchronic RfDs for neodymium compounds. However, only one of the studies (Haley et al., 1964) provides sufficient information to be considered quantitatively for the derivation. Hutcheson et al. (1975) provides quantitative

data —but only for mixtures of lanthanides. Bruce et al. (1963) provides information of the relative toxicity of neodymium compounds. Information on the toxicity of repeated oral exposure to neodymium in animals is limited to a single 90-day dietary study of neodymium chloride in rats (Haley et al., 1964). No effects were observed on the parameters evaluated (body weight, hematology and histopathology of selected tissues); thus, the highest dose tested (840 mg $NdCl_3$/kg-day or 483 mg Nd/kg-day in males; 950 mg $NdCl_3$/kg-day or 547 mg Nd/kg-day in females) was identified as a 90-day NOAEL for neodymium chloride. Developmental, reproductive, and chronic toxicity studies in animals were not identified. Use of the NOAEL from Haley et al. (1964) is supported by the fact that, even acutely, neodymium chloride does not seem to be unusually toxic by the oral route. Haley et al. (1964) also reported an acute oral LD_{50} of 3014 mg Nd/kg for neodymium chloride in male mice.

Different chemical forms of neodymium may have different toxic potencies. However, because only one repeated oral dose study on neodymium alone has been located, data with which to compare the subchronic or chronic oral toxicity of different neodymium compounds are not available. The only other data available on the oral toxicity of neodymium were acute oral LD_{50}s of 3014 mg Nd/kg for neodymium chloride in male mice (Haley et al., 1964) and 905 mg Nd/kg for neodymium nitrate in female rats (Bruce et al., 1963). Due to the limited information available, it is not possible to determine whether the differences in acute lethality for the chloride and nitrate compounds reflected differences in toxicokinetics of the neodymium compounds, differences in sensitivity of the animal species tested (mice vs. rats), gender differences, or other differences in experimental methods (see discussion under Acute Toxicity).

The limited available data do not provide assurance that a p-RfD based on data for neodymium chloride would be adequate for other neodymium compounds. While this document attempts to address the toxicity of the element neodymium, in light of the lack of information on relative oral toxicity of different neodymium compounds, available data supports derivation of a p-RfD only for the compound, neodymium chloride.

The subchronic oral toxicity study on neodymium chloride in rats conducted by Haley et al. (1964) serves as the critical study for derivation of the subchronic p-RfD. The NOAEL of 840 mg $NdCl_3$/kg-day or 483 mg Nd/kg-day in male rats is used to derive a **subchronic p-RfD for neodymium chloride** as follows:

$$\begin{aligned} \textbf{NdCl}_3\textbf{ Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 840 \text{ mg } NdCl_3\text{/kg-day} \div 1000 \\ &= 0.8 \text{ or } \mathbf{8 \times 10^{-1}\ mg\ NdCl_3/kg\text{-}day} \end{aligned}$$

AND

$$\begin{aligned} \textbf{NdCl}_3\textbf{ Subchronic p-RfD as Nd} &= 483 \text{ mg Nd/kg-day} \div 1000 \\ &= 0.5 \text{ or } \mathbf{5 \times 10^{-1}\ mg\ Nd/kg\text{-}day} \end{aligned}$$

The composite UF of 1000 is composed of the following:

- A default UF of 10 is applied for interspecies extrapolation to account for potential pharmacokinetic and pharmacodynamic differences between rats and humans.

- A default UF 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 full UF of 10 is applied for uncertainty in the database. The critical study used only six animals per dose group. There are no supporting toxicity, reproductive, or developmental studies on neodymium alone.

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

Confidence in the principal study (Haley et al., 1964) is low. Although both genders were tested in this study, small numbers of animals were used for each dose group (6/gender), resulting in the possibility that responses of ~10% or more likely would be missed. In addition, the estimate of food intake was not linked to the growth data, resulting in the possibility that a subtle effect of Nd on food intake could have been missed, leading to a biased estimate of dose. The toxicological evaluation in this study is 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 made. A LOAEL was not identified. Confidence in the database on neodymium is low. Apart from the critical study, the only other oral toxicity studies conducted on neodymium are acute lethality studies in rats and mice. Reproduction and developmental toxicity studies on neodymium are not available. A reproduction and developmental study on a mixture of lanthanide oxides (Hutcheson et al., 1975) indicates that the mixture did not affect reproduction or development; however, this study did not include neodymium in the mixture. Oral toxicokinetic data on neodymium are lacking; however, based on data on the gastrointestinal absorption of other lanthanide compounds, oral absorption of neodymium is expected to below. There are no data to indicate the toxicological endpoint(s) or target organ(s) of subchronic or chronic oral exposure to neodymium. Low confidence in the subchronic p-RfD follows.

A chronic p-RfD is not derived for neodymium. There are no studies of chronic exposure to any neodymium compound in any species. The uncertainties about the subchronic point of departure (POD) from the Haley et al. (1964) neodymium chloride feeding study preclude its extrapolation to chronic exposures. Toxicokinetic studies of lanthanide elements indicate 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 exhibits extremely slow retention kinetics (e.g. half-time exceeding 5 years in rats; Durbin et al., 1956). Although long-term skeletal retention of neodymium has not been evaluated, the potential for prolonged retention of neodymium 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, no chronic p-RfD is derived for any neodymium compound.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfCs FOR NEODYMIUM

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

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR NEODYMIUM

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to stable nonradioactive neodymium in humans or animals have not been identified in the available literature. Evidence of clastogenic activity was obtained from a study in mice showing an increase in the frequency of chromosomal aberrations in bone marrow cells of Swiss mice that were treated with single intraperitoneal doses of neodymium oxide. Under the 2005 *Guidelines for Cancer Risk Assessment* (U.S. EPA, 2005), there is "Inadequate Information to Assess [the] Carcinogenic Potential" of neodymium.

Quantitative Estimates of Carcinogenic Risk

The lack of carcinogenicity data precludes quantitative estimates of cancer risk for stable nonradioactive neodymium.

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