United States
Environmental Protection
Agency

EPA/690/R-09/048F
Final
9-17-2009

Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Praseodymium Chloride
(CASRN 10361-79-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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) PRASEODYMIUM CHLORIDE (CASRN 10361-79-2)

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

Praseodymium (Pr; CASRN 7440-10-0) is a rare earth element belonging to the lanthanide[1] series of the periodic table. Praseodymium compounds have been used in carbon-arc lamps for movie projection, alloys with high-strength metals, and in glass coloring. Praseodymium can form water-soluble compounds (e.g., praseodymium chloride and praseodymium nitrate) and insoluble compounds (e.g., praseodymium oxide and praseodymium hydroxide). Water-soluble praseodymium compounds (e.g., praseodymium 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 praseodymium and its compounds, and derives a toxicity value only for praseodymium chloride ($PrCl_3$). $PrCl_3$ typically is found as the heptahydrate (CASRN 10025-90-8).

The U.S. EPA IRIS (U.S. EPA, 2009) does not list an oral reference dose (RfD), inhalation reference concentration (RfC), or a cancer assessment for stable, nonradioactive praseodymium or any praseodymium compounds. Subchronic or chronic RfDs or RfCs for praseodymium are not listed in the 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 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 praseodymium. The American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2005). and the Occupational Safety and

[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).

Health Administration (OSHA, 2009) have not established occupational exposure limits for praseodymium. A toxicological review of the lanthanides is identified that derived toxicity values for several lanthanides—but not for praseodymium or its compounds (TERA, 1999).

Literature searches for studies relevant to the derivation of provisional toxicity values for praseodymium (CASRN 7440-10-0) 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 on October 22, 2008. 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 praseodymium 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) contend that, in general, 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); praseodymium 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 inhalation toxicity data on praseodymium 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; 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, floodlighting, printing, photoengraving, lithography, and electrowelding (Palmer et al., 1987).

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 gave 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 the details of diagnosis and medical follow-up. Interpretation of the human cases also are 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 praseodymium (or any other individual element) to the development of pneumoconiosis has not been established. 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.

---

[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).

Animal Studies

Oral Exposure—Praseodymium and Compounds

Only one repeated dose oral study of praseodymium alone (without other rare earth compounds) has been identified in the literature search. Haley et al. (1964) fed groups of six male and six female CRW rats 0, 0.01, 0.1, or 1% praseodymium chloride (purity not reported) in the diet for 90 days. Compound intake is estimated to be 8.4, 84, or 840 mg/kg-day (4.8, 48, or 479 mg Pr/kg-day) in the males, and 9.5, 95, or 950 mg/kg-day (5.4, 54, or 541 mg Pr/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 food consumption estimates of 0.026 kg/day and 0.020 kg/day for males and females, respectively[7]. Body weight and hematology (total erythrocytes, total leucocytes, differential cell counts, platelets, hemoglobin, and hematocrit) were measured biweekly, and histological examinations of the 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 90-day freestanding NOAEL of 840 mg/kg-day for praseodymium chloride (479 mg Pr/kg-day) in males and 950 mg/kg-day for praseodymium chloride (541 mg Pr/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 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, but not praseodymium, 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 1 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.

Hutcheson et al. (1975) reported neither dose nor food intake during the study. Therefore, daily doses of the 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 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

[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]Food consumption rates calculated based on allometric equation relating food consumption to body weight (U.S. EPA, 1988).
[8]Neutron bombardment creates traceable radioactive forms of the various compounds after the experiment is terminated.

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, blood was collected 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).

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 five samples.

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.

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 $p = 0.69$.

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 praseodymium 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 praseodymium pharmacokinetics or toxicity.

Inhalation Exposure—Praseodymium and Compounds

There were no inhalation studies of praseodymium 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 nine 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 also was 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 praseodymium 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. (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 et al. (1987) that chronic occupational exposure to stable rare earth dusts results in progressive pulmonary fibrosis. 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 forms, doses, and durations of exposure. In any case, the relevance of studies by Schepers (1955a,b; Schepers et al., 1955) to praseodymium toxicity is uncertain due to the lack of information on specific exposure concentrations and the praseodymium content of the mixtures.

Other Studies

Acute Exposure

Acute Lethality Studies—Acute oral lethality studies have been conducted for praseodymium chloride and praseodymium nitrate (see Table 4). Haley et al. (1964) reported an oral LD_{50} of 2565 mg Pr/kg for praseodymium chloride 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 or intraperitoneal exposure to

praseodymium chloride. No further details were provided and no other information on the potential neurotoxicity of praseodymium or other rare earth metals was identified in the literature search or reviews. Bruce et al. (1963) reported a lower oral LD_{50} of 1134 mg Pr/kg for praseodymium nitrate (administered by stomach tube in 50% aqueous solution) in female Sprague-Dawley rats (adults, 190−250 g).

Table 4 summarizes data from the intraperitoneal acute lethality studies conducted for praseodymium chloride, nitrate, citrate, and edetate compounds. For praseodymium chloride, LD_{50}s ranged from 71 mg Pr/kg in guinea pigs (300−500 g in weight, age, gender, and strain not reported) (Graca et al., 1957) to 342 mg Pr/kg in male CF1 mice (Haley et al., 1964). Graca et al. (1962) noted precipitate at the injection site of animals receiving intraperitoneal injections of praseodymium chloride, indicating that absorption was incomplete. Bruce et al., 1963) reported similar intraperitoneal LD_{50}s in female Sprague-Dawley rats (79 mg Pr/kg) and female CF1 mice (94 mg Pr/kg) for praseodymium nitrate.

Graca et al. (1962) tested the acute lethality of praseodymium 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 $PrCl_3$/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 $PrCl_3$ equivalents, or if all of the test materials were complexes of praseodymium chloride. As a consequence of this uncertainty, the LD_{50}s reported by Graca et al. (1957, 1962) are not considered to be reliable indicators of the acute toxicity of the citrate and edetate compounds. As reported by Graca et al. (1957, 1962), i.p. LD_{50}s for the praseodymium citrate complex were 140.6 to 145.28 mg $PrCl_3$/kg in CFW albino mice (age and gender not reported) and 53.0 to 75.3 mg $PrCl_3$/kg in guinea pigs (age, strain and gender not reported); an i.p. LD_{50} for praseodymium edetate complex was not reported in mice, but the LD_{50} in guinea pigs was 85.33 mg $PrCl_3$/kg (Graca et al, 1962). These LD_{50}s should be interpreted cautiously, given the uncertainties outlined above.

Table 4. Acute Lethality of Stable Praseodymium Compounds Following Oral and Parenteral Exposure

Compound	Species/Strain (Gender)	Route of Exposure	LD_{50} in mg Pr/kg Body Weight[a]	Reference
Praseodymium chloride	Mice/CF1 (male)	oral (not specified)	2565 (2311−2847)	Haley et al., 1964
	Mice/CF1 (male)	i.p.	342 (315−372)	Haley et al., 1964
	Mice/CFW albino (NR)	i.p.	205 (169−247)[b]	Graca et al., 1957
	Guinea pigs/NR (NR)	i.p.	71 (44−114)[b]	Graca et al., 1957
Praseodymium nitrate	Rats/Sprague-Dawley (female)	oral (gavage, 50% aqueous solution)	1134 (977−1315)	Bruce et al., 1963
	Mice/CF1 (female)	i.p.	94 (84−105)	Bruce et al., 1963
	Rats/Sprague-Dawley (female)	i.p.	79 (68−93)	Bruce et al., 1963
	Rats/Sprague-Dawley (female)	i.v.	2.1 (1.8−2.4)	Bruce et al., 1963
	Rats/Sprague-Dawley (male)	i.v.	25 (16−39)	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.

Bruce et al. (1963) reported intravenous LD_{50}s of 25 and 2.1 mg Pr/kg in male and female Sprague-Dawley rats, respectively, for praseodymium nitrate, suggesting 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 and cerium 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 praseodymium compounds. As noted earlier, the available LD_{50}s for edetate and citrate forms of praseodymium (Graca et al., 1957, 1962) cannot be considered reliable due to

uncertainty in the reported doses. The intravenous lethality data also were 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 praseodymium chloride in mice and guinea pigs and praseodymium nitrate in mice and rats suggest that the acute i.p. toxicity of these praseodymium compounds is of comparable order of magnitude; LD_{50}s ranged between 94 and 342 mg Pr/kg-day. It should be noted that the one mouse i.p. LD_{50} for praseodymium nitrate is for female mice, while the LD_{50}s for praseodymium chloride are for male mice (Haley et al., 1964) or for mice of unspecified gender (Graca et al., 1957). Because gender differences in the acute lethality of some rare earth compounds has been noted (Wells and Wells, 2001), and gender differences in the acute i.p. lethality of praseodymium nitrate were observed in rats (Bruce et al., 1963), 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 praseodymium chloride (Graca et al., 1957), the absorption of praseodymium chloride may have been affected by the formation of insoluble hydroxides or protein complexes at the injection site.

The oral acute toxicity data for praseodymium chloride and praseodymium 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. 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, greater oral toxicity of the praseodymium nitrate might be inferred from the properties of the nitrate anion. However, the behavior of praseodymium 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 praseodymium.

Data on the acute oral or parenteral toxicity of insoluble praseodymium 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 rare earth 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. Ten doses of 10 mg/kg each (as the chloride or its equivalent in the chelates) were injected at 10-minute intervals. For each element, nine dogs were divided into groups of three, each injected with the chloride, citrate, or edetate. 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 intravenously than the citrate or edetate compounds. One hour after injection, praseodymium chloride produced a ~10% decrease in blood pressure, with a ~35% decrease at 100 minutes and ~40% at 160 minutes after injection. Graca et al. (1964) observed similar effects on blood pressure for praseodymium citrate and edetate, for which blood pressure at the 10- and 30-minute observations also was decreased approximately 5−20%. Injection of praseodymium chloride produced decreases in heart rate that progressed over time by approximately 8% at 10 minutes to approximately 20−25% at ≥100 minutes. Graca et al. (1964) observed similar effects for praseodymium edetate, although decreases were slightly less than those observed for the chloride. For praseodymium citrate, heart rate decreased slightly (approximately 5−10%) from 10 to 100 minutes, but it increased by approximately 30% at 160 minutes after injection. Respiration rate was increased at all time points for all praseodymium compounds, with the most pronounced change observed in animals injected with praseodymium citrate (approximately 30 to 50% 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 to 10 seconds in controls to >100 seconds for praseodymium chloride, 35 to 100 seconds for praseodymium citrate and 20 to 30 seconds for praseodymium edetate. Compared to coagulation times in controls (approximately 10 minutes), coagulation times were increased to >60 minutes for praseodymium chloride and praseodymium citrate (approximately 18 to >100 minutes); effects on clotting time for praseodymium edetate were only observed at the 160-minute observation point (>60 minutes). Effects of praseodymium 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 injected with chlorides of the rare-earth elements.

Several studies have used intravenous injection of praseodymium nitrate or chloride in rats as an experimental model for liver injury (Schurig and Oberdisse, 1972; Schriewer et al., 1976; Tuchweber et al., 1976; von Lehmann et al., 1975, 1976; Oberdisse et al., 1979; Oga et al., 1986). Typical doses used to induce hepatotoxic effects were 5−10 mg/kg for praseodymium nitrate (2.2−4.3 mg Pr/kg) and praseodymium chloride (2.8−5.7mg Pr/kg). Hepatotoxic effects of intravenously injected praseodymium included fatty degeneration, changes in hepatic microsomal lipid content, decreased RNA polymerase activity, and inhibition of gluconeogenesis and drug metabolizing enzymes.

Toxicokinetics

Based on the available data for other light lanthanides, praseodymium 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 praseodymium 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 Praseodymium and Compounds—Studies evaluating the toxicokinetics of oral or inhaled praseodymium in humans or animals have not been identified. Durbin et al. (1956) investigated the distribution and elimination of ^{143}Pr in groups of five female Sprague-Dawley rats following intramuscular injection of 180 μCi of ^{143}Pr-labeled praseodymium oxide (specific form of compound not reported; no carrier used; dose not reported). Distribution and elimination of radioisotopes of 14 other lanthanide elements also were investigated in the same study. Urine and feces were collected for 4 days after administration; selected tissues were analyzed for ^{143}Pr upon sacrifice 4 days after dosing. Approximately 22% and 60% of the administered ^{143}Pr were distributed to the bone and liver, respectively, and approximately 8% was excreted in urine and feces after 4 days (data presented graphically); the distribution of the remaining 10% of the administered dose was not reported. The initial distribution of praseodymium was similar to that observed for other light lanthanide elements. Although Durbin et al. (1956) did not evaluate the long-term skeletal retention of ^{143}Pr in the study, skeletal retention curves for other the light lanthanide elements (^{147}Pm and ^{144}Ce) showed two components, a labile component and a fixed component. 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 praseodymium were unavailable. However, it should be noted that such long-term deposition of radioactive praseodymium 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 praseodymium.

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 praseodymium 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). Praseodymium chloride ($PrCl_3$) is a relatively strong Lewis acid that forms insoluble hydroxides at neutral or alkaline pH; these reactions may limit the bioavailability of ingested praseodymium chloride, relative to more water-soluble praseodymium salts such as praseodymium 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. Nose-only exposures were 30 minutes for rats (strain and gender not reported) and whole body exposures were 5 to 10 minutes 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, kidneys, gastrointestinal tract, gonads, hepatic lymph nodes, tracheobronchial lymph nodes, heads, pelts, skeleton, and muscles. 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 inhalation exposure to be 1.05 μg Sm_2O_3; initial lung burdens in dogs were 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 distributions 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 contained 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 2 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 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 praseodymium, 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 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 the interpretation of data from bioassays.

Genotoxicity

There is limited evidence that praseodymium has genotoxic activity. Exposure of human lymphocytes to nonradioactive praseodymium chloride in vitro produced a concentration-related increase in the frequency of micronuclei (Hui et al., 1998). Nonradioactive praseodymium 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 5.1−38.5 mg/100 g, equivalent to 7.0−53 mg Pr/kg (Jha and Singh, 1995). A maximum effect of 4-fold compared to negative controls was observed in cells harvested 12 hours postexposure.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfDs FOR STABLE PRASEODYMIUM CHLORIDE

Data on the oral toxicity of subchronic or chronic human exposure to stable praseodymium compounds have not been identified. Three animal studies were identified that have the potential to inform derivation of provisional subchronic RfDs for praseodymium 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 praseodymium compounds. Information on the toxicity in experimental animals of repeated oral exposure to praseodymium alone (e.g., not as part of a mixture with other lanthanide compounds) is limited to a single subchronic dietary study on praseodymium 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 $PrCl_3$/kg-day or 479 mg Pr/kg-day in males; 950 mg $PrCl_3$/kg-day or 541 mg Pr/kg-day in females) was identified as a 90-day NOAEL for praseodymium 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, praseodymium chloride does not seem to be unusually toxic by the oral route. Haley et al. (1964) also reported an oral LD_{50} of 2565 mg Pr/kg for praseodymium chloride in male CF1 mice.

Different chemical forms of praseodymium may have different toxic potencies. However, because a repeated oral dose study was located only for praseodymium chloride, data with which to compare the subchronic or chronic oral toxicities of different praseodymium compounds are not available. The only other data available on the oral toxicity of praseodymium are acute oral LD_{50}s of 2565 mg Pr/kg for praseodymium chloride in male mice (Haley et al.,

1964) and 1134 mg Pr/kg for praseodymium 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 praseodymium 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 praseodymium chloride would be adequate for other praseodymium compounds. While this document attempts to address the toxicity of the element praseodymium, in light of the lack of information on relative oral toxicity of different praseodymium compounds, available data supports derivation of a subchronic p-RfD only for the compound, praseodymium chloride.

The subchronic oral toxicity study on praseodymium 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 $PrCl_3$/kg-day or 479 mg Pr/kg-day in male rats is used to derive a **subchronic p-RfD for praseodymium chloride** as follows:

$PrCl_3$ Subchronic p-RfD	=	NOAEL ÷ UF
	=	840 mg $PrCl_3$/kg-day ÷ 1000
	=	0.8 or **8×10^{-1} mg $PrCl_3$/kg-day**
$PrCl_3$ Subchronic p-RfD as Pr	=	479 mg Pr/kg-day ÷ 1000
	=	0.5 or **5×10^{-1} mg Pr/kg-day**

The composite UF of 1000 is composed of the following:

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

Given the uncertainties regarding relative potencies of praseodymium compounds, this subchronic p-RfD should be applied only to praseodymium chloride.

Confidence in the principal study (Haley et al., 1964) is low. Although both genders were tested in this study, a small number 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 praseodymium 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 subchronic database on praseodymium is low.

Apart from the critical study, the only other oral toxicity studies conducted on praseodymium are acute lethality studies in rats and mice. Reproduction and developmental toxicity studies on praseodymium 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 praseodymium in the mixture. Toxicokinetic data on oral praseodymium are lacking; however, it is anticipated that oral absorption of praseodymium chloride would be low, based on data on the gastrointestinal absorption of other lanthanide compounds. Although intravenous exposure has been shown to produce liver injury in rats, there are no data indicating what, if any toxicological endpoints or target organ effects result from repeated oral exposure to praseodymium chloride. Low confidence in the subchronic p-RfD results.

A chronic p-RfD is not derived for praseodymium or any of its compounds. Studies evaluating the effects of chronic exposure of stable praseodymium compounds have not been located. The uncertainties about the subchronic POD from the Haley et al. (1964) praseodymium 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 praseodymium has not been evaluated, the potential for prolonged retention of praseodymium 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 discussed above, no chronic p-RfD is derived for any praseodymium compound.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfCs FOR PRASEODYMIUM

Studies investigating the effects of inhalation exposure of humans and animals are limited to evaluations on mixtures of rare earth metals containing praseodymium. 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 data precludes derivation of subchronic and chronic p-RfCs for praseodymium.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PRASEODYMIUM

Weight-of-Evidence Descriptor

Studies evaluating the carcinogenic potential of oral or inhalation exposure to praseodymium in humans or animals have not been located 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 nonradioactive praseodymium oxide and a study showing micronucleus formation in treated human lymphocytes in vitro. 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) praseodymium provided "Inadequate Information to Assess [the] Carcinogenic Potential" of praseodymium or its compounds.

Quantitative Estimates of Carcinogenic Risk

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

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2008. 2008 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 2009. Toxicological Profile Information Sheet. Viewed online, July 2009 at http://www.atsdr.cdc.gov/toxprofiles/index.asp.

Bruce, D.W, B.E. Hietbrink, and K.P. DuBois. 1963. The acute mammalian toxicity of rare earth nitrates and oxides. Toxicol. Appl. Pharmacol. 5:750−759.

Colombo, F., M. Zanoni, G. Vocaturo et al. 1983. Pneumoconiosi da terre rare. (Pneumoconiosis due to rare earth metals). Med. Lav. 74:191−197.

Deng, J.F., T. Sinks, L. Elliott, D. Smith, M. Singal and L. Fine. 1991. Characterization of respiratory health and exposures at a sintered permanent magnet manufacturer. J. Ind. Med. 48:609−615.

Durbin, P.W., M.H. Williams, M. Gee et al. 1956. Metabolism of the lanthanons in the rat. Proc. Soc. Exp. Biol. Med. 91:78−85.

Fairweather-Tait, S.J., A.-M. Minihane, J. Eagles et al. 1997. Rare earth elements as nonabsorbable fecal markers in studies of iron absorption. Am. J. Clin. Nutr. 65:970−976.

Graca, J.G., E.L. Garst, W.E. Lowry. 1957. Comparative toxicity of stable rare earth compounds. A.M.A. Arch. Ind. Health. 15:9−14.

Graca J.G., F.C. Davison and J.B. Feavel. 1962. Comparative toxicity of stable rare earth compounds: II. Effect of citrate and edetate complexing on acute toxicity in mice and guinea pigs. Arch. Environ. Health. 5:437−450.

Graca J.G., F.C. Davison and J.B. Feavel. 1964. Comparative toxicity of stable rare earth compounds: III. Acute toxicity of intravenous injections of chlorides and chelates in dogs. Arch. Environ. Health. 8:555−564.

Haley, P.J. 1991. Pulmonary toxicity of stable and radioactive lanthanides. Health Physics. 61:809−821.

Haley, T.J. 1965. Pharmacology and toxicology of the rare earth elements. J. Pharm. Sci. 54(5):663−670.

Haley, T.J., N. Komesu, M. Efros et al. 1964. Pharmacology and toxicology of praseodymium and neodymium chlorides. Toxicol. Appl. Pharmacol. 6:614−620.

Hirano, S. and K.T. Suzuki. 1996. Exposure, metabolism and toxicity of rare earths and related compounds. Environ. Health Perspect. 104(Suppl 1):85−95.

Hui, Y., J. Qing, and Z. Xiran. 1998. Studies on effects of yttrium chloride and praseodymium chloride on frequency of micronucleus in human blood lymphocytes. Zhong. Yuf. Yix. Zaz. 32(3):156−158. (Article in Chinese with an English abstract).

Husain, M.H., J.A. Dick, and Y.S. Kaplan. 1980. Rare earth pneumoconiosis. J. Soc. Occup. Med. 30:15−19.

Hutcheson, D.P., D.H. Gray, B. Venugopal et al. 1975. Studies of nutritional safety of some heavy metals in mice. J. Nutr. 105:670−675.

IARC (International Agency for Research on Cancer). 2009. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Viewed online, July 2009 at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php.

ICRP (International Commission on Radiological Protection). 1981. Metabolic Data for: Praseodymium and Samarium. Limits for Intakes of Radionuclides by Workers. Pergamon Press: New York, NY. ICRP Publication 30, Part 3:53−63.

ICRP (International Commission on Radiological Protection). 1983. Radionuclide Transformations: Energy and Intensity of Emissions. ICRP Publication 38. Report of a Task Group of Committee 2 of the International Commission on Radiological Protection on data used in ICRP Publication 30. Published for the International Commission on Radiological Protection by the Pergamon Press. New York. 1250 pages.

Jha, A.M. and A.C. Singh. 1995. Clastogenicity of lanthanides: Induction of chromosomal aberration in bone marrow cells of mice in vivo. Mutat. Res. 341:193−197.

Kappenberger, L. and A.A. Buhlmann. 1975. Lungenveranderungen durch "seltene erden." (Lung lesions caused by "rare earths"). Schweiz. Med. Wochenschr. 105:1799−1801.

Kirk-Othmer. 1995. "Lanthanides" IN Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Edition. Volume 14: Imaging Technology to Lanthanides. John Wile & Sons. New York. p. 1091−1115.

Mode, V.A. 1990. Review of the literature on the toxicity of rare-earth metals as it pertains to the engineering demonstration system surrogate test. Revision 1. Lawrence Livermore National Laboratory, University of California, Livermore, CA.

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. Viewed online, July 2009 at http://www.cdc.gov/niosh/npg/npgsyn-a.html.

NTP (National Toxicology Program). 2005. 11th Report on Carcinogens. Online. http://ntp.niehs.nih.gov/ntp/roc/toc11.htm.

NTP (National Toxicology Program). 2009. Management Status Report. Viewed online, July 2009.

Oberdisse, E., P. Arvela, and U. Gross. 1979. Lanthanon-induced hepatotoxicity and its prevention by pretreatment with the same lanthanon. Arch. Toxicol. 43:105−114.

Oga, S., J.F. Galvao, W.J. Yasaka et al. 1986. Effect of praseodymium chloride on liver microsomal enzymes of rats. Life Sci. 38:2029−2036.

OSHA (Occupational Safety and Health Administration). 2009. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Viewed online, July 2009 at https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992.

Palmer R.J., J.L. Butenhoff, and J.B. Stevens. 1987. Cytotoxicity of the rare earth metals cerium, lanthanum, and neodymium in vitro: comparisons with cadmium in a pulmonary macrophage primary culture system. Environ Res. 43:142−156. Cited in Haley et al. (1991).

Sabbioni, E., R. Pietra, P. Gaglione et al. 1982. Long-term occupational risk of rare-earth pneumoconiosis: A case report as investigated by neutron activation analysis. Sci. Total Environ. 26:19−32.

Schepers, G.W.H. 1955a. The biological action of rare earths. II. The experimental pulmonary histopathology produced by a blend having a relatively high fluoride content. A.M.A. Arch. Ind. Health. 12:306−316.

Schepers, G.W.H. 1955b. The biological action of rare earths. I. The experimental pulmonary histopathology produced by a blend having a relatively high oxide content. A.M.A. Arch. Ind. Health. 12:301−305.

Schepers, G.W.H., A.B. Delahant, and A.J. Redlin. 1955. An experimental study of the effects of rare earths on animal lungs. A.M.A. Arch. Ind. Health. 12:297−300.

Schriewer, V.H., B. Gebauer, and H.M. Rauen. 1976. Die akute leberschaadigung der ratte mit praseodynmitrat [Acute liver injury in rats by praseodymium nitrate]. Arzneim. Forsch. 26:399−402.

Schurig, R. and E. Oberdisse. 1972. The influence of rare earths on hepatic gluconeogenesis. Nauyn-Schmiedeberg's Arch. Pharmacol. 275:419−433.

Shipler, D.B., J.E. Ballou, B.I. Griffin et al. 1975. Development of a diagnostic model for inhaled ^{147}promethium oxide—animals studies. Battelle, Pacific-Northwest Laboratory. Richland, Washington. Document Number BNWL-SA-5464.

Sullivan, M.F., P.S. Ruemmlier, J.L. Ryan et al. 1986. Influence of oxidizing or reducing agents on gastrointestinal absorption of U, Pm, Am, Cm and Pm by rats. Health Phys. 50(2):223−232.

Sulotto, F., C. Romano, A. Berra et al. 1986. Rare-earth pneumoconiosis: A new case. Am. J. Ind. Med. 9:567−575.

Taylor, D.M. and R.W. Leggett. 2003. A generic biokinetic model for predicting the behaviour of the lanthanide elements in the human body. Radiat. Prot. Dosim. 105(1−4):193−198.

TERA (Toxicology Excellence for Risk Assessment). 1999. Development of Reference Doses and Reference Concentrations for Lanthanides. Prepared for: U.S. Bureau of Land Management, National Applied Resource Sciences Center. Viewed online, July 2009 at http://www.tera.org/Publications/Lanthanides.pdf.

Tuchweber, B., R. Trost, M. Salas et al. 1976. Effect of praseodymium nitrate on hepatocytes and Kuppffer cells in the rat. Can. J. Physiol. Pharmacol. 54:898−906.

Ulusoy, U. and J.E. Whitley. 2000. Profiles of faecal output of rare earth elements and stable isotopic tracers of iron and zinc after oral administration. Br. J. Nutr. 84:605−617.

U.S. EPA (U.S. Environmental Protection Agency). 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Environmental Criteria and Assessment Office, Cincinnati, OH. NTIS PB179874. Viewed online, July 2009 at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared for the Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB 97-921199.

U.S. EPA. 2005. Guidelines for Cancer Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001F. Viewed online, July 2009 at http://www.epa.gov/cancerguidelines/.

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA/822/R-06/013. Viewed online, July 2009 at http://water.epa.gov/drink/standards/hascience.cfm.

U.S. EPA. 2009. Integrated Risk Information System (IRIS). Viewed online, July 2009 at Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Viewed online, July 2009 at http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList.

Vocaturo, G., F. Colombo, M. Zanoni, et al. 1983. Human exposure to heavy metals: Rare earth pneumoconiosis in occupational workers. Chest. 83:780−783.

Vogt, P., M.A. Spycher and J.R. Ruttner. 1986. Pneumokoniose durch "seltene erden" (cer-pneumokoniose). [Pneumoconiosis caused by "rare earths" (cer-pneumoconiosis)]. Schweiz. Med. Wochenschr. 116:1303−1308.

von Lehmann, B., E. Oberdisse, O. Grajewski et al. 1975. Subcellular distribution of phospholipids during liver damage induced by rare earths. Arch. Toxicol. 34:89−101.

von Lehmann, B., O. Grajweski, H.R. Arntz et al. 1976. Correlation between serum high density lipoprotein content and liver function during experimental hepatic degeneration and regeneration. Act. Hepato-Gastroenterol. 24:328−333.

Waring, P.M. and R.J. Watling. 1990. Rare earth deposits in a deceased movie projectionist: A new case of rare earth pneumoconiosis. Med. J. Aust. 153:726−730.

Wells W.H. and V.L. Wells. 2001. The Lanthanides, Rare Earth Metals. In: Patty's Industrial Hygiene and Toxicology, Fifth Edition, Volume 3, E. Bingham, B Cohrssen, and C.H. Powell, ed. John Wiley and Sons, Inc., New York, NY. p. 423−458.

WHO (World Health Organization). 2009. Environmental Health Criteria Monographs. Accessed online Viewed online, July 2009 at http://www.inchem.org/pages/ehc.html.