Development of Reference Doses and Reference Concentrations for Lanthanides

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1.0 Introduction

1.1 Existing Reference Doses (RfDs) and Concentrations (RfCs)

This document addresses the development of an RfD and/or an RfC for the non-cancer, non-radiological risk assessments for the rare earth elements known as the Lanthanides. This mixture may include such rare earth elements as neodymium (Nd), cerium (Ce), scandium (Sc), yttrium (Y), dysprosium (Dy) and lanthanum (La). Currently, the U.S. EPA's Integrated Risk Information System (IRIS) database does not list any risk assessment values for either the mixture known as the lanthanides or the individual rare earth metals including any of their respective salts. No EPA documentation for any of these elements characterized as lanthanides was located on IRIS or HEAST. This document presents the development of an RfD for the chlorides of lanthanum, europium, and yttrium and the oxides of lanthanum, europium and scandium and the development of an RfC for the oxides of cerium and gadolinium.

1.2 Purpose of This Document

The purpose of this project is to develop non-radiological, non-cancer risk assessment for the oral and/or inhalation routes of exposure on the rare earth mixture known as the lanthanides, and in particular a mixture composed primarily of lanthanum and cerium. This mixture is the primary material mined by Molycorp at the Mountain Pass Mine site, Mountain Pass, California.

This document was preceded by an earlier text, where *TERA* conducted appropriate literature reviews to identify any studies that are likely to have had a bearing on the development of RfDs and RfCs for these lanthanides. This literature was reviewed, and *TERA* developed a brief summary of the database as it pertains to these noncancer risk assessments (TERA, 1999). We now show what are likely to be the definitive critical studies for the development of these RfDs and RfCs, and describe the areas of scientific uncertainty that require the use of uncertainty factors. Specific values for these lanthanides are proposed.

1.3 The Methods Used

The RfD/RfC methods of U.S. EPA were used to evaluate and quantify the non-cancer toxicity of the lanthanides. The determination of RfD/RfCs lies squarely in the area of hazard identification and dose response assessment as defined by the National Research Council of the National Academy of Sciences (NRC, 1983) report on risk assessment in the federal government. EPA defines the reference concentration (or reference dose) as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous (or daily) exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. (Barnes and Dourson, 1988; Dourson, 1994; Jarabek, 1994; U.S. EPA, 1994).

For health effects that are not cancer, the EPA and others first identify the critical effect(s), which is the first adverse effect(s) or its known precursor that occurs in the dose scale. Human toxicity data adequate for use in the estimation of RfD/RfCs are seldom available, but if so, they are preferred in the selection of this critical effect. The use of human data has the advantage of avoiding the uncertainties inherent in interspecies extrapolation.

After the critical effect(s) has been identified, EPA generally selects an experimental exposure level from a study that represents the highest level tested at which the critical effect was not demonstrated. This level, the No Observed Adverse Effect Level (NOAEL), is the key datum gleaned from the toxicologist's review of the chemical's entire database and is the first component in the estimation of a RfC. If a NOAEL is not available, the use of a Low Observed Adverse Effect Level (LOAEL) is recommended. Alternatively, a benchmark concentration (BMC) (or benchmark dose, BMD) may be used in this part of the assessment. A BMC/BMD is a statistical lower confidence limit on the concentration that produces a predetermined level of change in adverse response compared with the response in untreated animals (called the benchmark response or BMR). Advantages and disadvantages of NOAELs and BMDs/BMCs are described elsewhere (U.S. EPA, 1995).

Presented with data from several animal studies, EPA first seeks to identify the animal model that is most relevant to humans, based on the most defensible biological rationale, for example using comparative pharmacokinetic data. In the absence of a clearly most relevant species, however, EPA generally chooses the critical study and species that shows an adverse effect at the lowest administered dose. This is based on the assumption that, in the absence of data to the contrary, humans may be as sensitive as the most sensitive experimental animal species.

The above discussion applies to both the development of RfDs and RfCs. For RfCs, there are several additional steps. Exposure levels in ppm are converted to mg/cu.m using the equation:

$$1 \text{ mg/cu.m} = 1 \text{ ppm} \times \text{MW}/24.45 \text{ cu.m}$$

The factor of 24.45 is the volume occupied by 1 mole of an ideal gas at 1 atmosphere of pressure and 25 degrees Celsius.

In the next step, exposure levels are adjusted to account for the fact that the RfC is defined based on continuous exposure, but many inhalation toxicity studies in experimental animals are conducted using a discontinuous exposure regiment, such as 6 hours/day, 5 days/week. To account for this difference, exposures are normalized to account for discontinuous exposure. Mathematically:

$$\text{NOAEL}^*_{[\text{ADJ}]} \text{ (mg/cu.m)} = \text{E mg/cu.m} \times \text{D (hours/24 hours)} \times \text{W (days/7 days)}$$

where the NOAEL* is the NOAEL or analogous effect level, such as the benchmark concentration, E is the exposure level, D is the number of hours exposed per day, and W is the number of exposure days per week.

When extrapolating from occupational exposures, adjustments are made both for discontinuous exposure and for the higher ventilation rate under occupational conditions. Human equivalent concentrations for ambient exposure are calculated from occupational exposure levels by adjusting for the number of exposure days per week, as well as for the differences between the default human occupational minute volume (VEho, 10 m^3 per 8 hour day) and the human ambient default minute volume (VEh, 20 m^3 per 24 hour day):

$$NOAEL^*_{[HEC]}\ (mg/m^3) = NOAEL\ (mg/m^3) \times (VEho/VEh) \times 5\ days/7\ days$$

where $NOAEL^*_{[HEC]}$ is the human equivalent concentration for the assumed ambient scenario or an analogous effect level, the NOAEL is the time-weighted-average (TWA) occupational exposure level, VEho is the human occupational default minute volume (10 m^3 per 8 hour day), and VEh is the human ambient default minute volume (20 m^3 per 24 hour day).

The final RfC-specific step is conducting dosimetric adjustments to calculate human equivalent concentrations. For gases, the dosimetric approach used is based on consideration of the target region (respiratory or extrarespiratory, and whether in the extrathoracic, tracheobronchial, or pulmonary region of the respiratory tract), as well as the chemical's mode of action. Based on these considerations, the chemical is classified into one of three categories. Gases that do not penetrate to the blood are considered category 1. These gases are highly water soluble and/or rapidly reactive, and thus exert most of their toxic effects in the respiratory tract. HECs are calculated for category 1 gases based on animal and human minute volumes and surface areas of the respiratory tract, taking into account the "scrubbing" that occurs at higher levels of the respiratory tract and reduces penetration to lower levels. Category 3 gases are fairly insoluble in water, and are not chemically reactive. Thus, these chemicals do not deposit or react appreciably in the extrathoracic or tracheobronchial regions, and instead primarily cause extrarespiratory effects. HECs for category 3 gases, or extrarespiratory effects of category 1 gases, are calculated based on the blood:air partition coefficient of the chemical in the experimental animal species of interest and in humans. Category 2 gases fall between categories 1 and 3.

Inhalation exposures to the lanthanides in complex or individually are to the particulate form, for which a different dosimetric adjustment is used. For particles, human equivalent concentrations are calculated based on particle deposition in the respiratory tract region of interest, the ventilation rate, and the regional surface area. These calculations are conducted using EPA's Regional Deposited Dose Ratio (RDDR) model (U.S. EPA 1994). Required inputs for the model are the mass median aerodynamic diameter (MMAD), and the geometric standard deviation (sigma g), which together describe the particle size distribution for the particle or aerosol of interest; as well as the animal species and body weight. The human equivalent concentration is calculated using the equation:

$$NOAEL^*_{[HEC]}\ (mg/m^3) = NOAEL^*_{[ADJ]}\ (mg/m^3) \times RDDR_r$$

where the Regional Deposited Dose Ratio for region r is calculated by the RDDR model (U.S. EPA, 1994). The potential respiratory tract regions are the extrathoracic (ET), tracheobronchial (TB), or pulmonary (PU). Combined regions for which the $RDDR_r$ can also be calculated are the thoracic (TH) region (TB plus PU regions) and the total (TOT) respiratory tract (all three respiratory tract regions). The RDDR can also be calculated for extrarespiratory (ER) effects. For extrarespiratory (systemic) effects, total deposition (deposition summed for all three regions) is assumed to be available for transport to other organs.

In the absence of adequate human data EPA generally considers a "complete" database, that is, complete for the purpose of calculating a RfC for noncancer health effects, to be composed of:

- two adequate mammalian chronic inhalation toxicity studies in different species that included evaluation of the respiratory tract;
- one adequate mammalian multi-generation reproductive toxicity study by an appropriate route; and
- two adequate mammalian developmental toxicity studies by an appropriate route in different species.

A “complete” database for the purposes of developing an RfD is similar. An adequate study is one that tests a sufficient number of animals of both sexes at two or more nonzero dose levels, and was adequately performed and documented. In addition, the study should ideally identify an effect level (i.e., a LOAEL). If no LOAEL is identified, the study can still be considered adequate if it tested doses well above the critical effect that forms the basis for the RfD or RfC. (For example, a developmental study in which the high concentration was10x the NOAEL for the principal study, but that found no effects, would be considered adequate.) The determination of study adequacy rests on professional judgment. A detailed discussion of the factors to be considered when evaluating the adequacy of a database and a study can be found in U.S. EPA (1994).

Uncertainty factors (UFs) are reductions in the dose rate or concentration to account for areas of scientific uncertainty inherent in most toxicity databases. The choice of appropriate uncertainty and modifying factors reflects a case-by-case judgment by experts and should account for each of the applicable areas of uncertainty and any nuances in the available data that might change the magnitude of any factor.

Typically, EPA uses uncertainty factors to account for five areas of uncertainty. The UF for human variability (designated as H) is intended to account for the variation in sensitivity among the members of the human population. The UF for experimental animal-to-human extrapolation (designated as A) is intended to account for the extrapolation from animal data to the case of humans and is considered to have components of both toxicokinetics and toxicodynamics. The subchronic-to-chronic UF (designated as S) is intended to account for extrapolating from less than chronic levels to chronic levels. The UF for LOAEL-to-NOAEL extrapolation (designated as L) is applied when an appropriate NOAEL is not available to serve as the basis for a risk estimate, and extrapolation from an experimental LOAEL is necessary.

Database completeness (designated as D) is intended to account for the inability of any single study to adequately address all possible adverse outcomes. EPA currently uses an additional factor, referred to as a modifying factor (MF), as an occasional adjustment in the estimation of an RfD/RfC to account for areas of uncertainty not explicitly addressed by the usual factors.

The traditional default value of 10 has been generally used for each of these UFs. EPA, however, through experience of calculating thousands of RfD/RfCs, has developed criteria for reducing UFs (generally to a half-log value of 3, or 1), when data warrant. EPA also recognizes the potential overlap between UFs and attempts to accommodate this. In particular, the standard practice is to use a factor of 3 for interspecies extrapolation when developing a RfC using the standard dosimetric adjustments (U.S. EPA, 1994). A recent publication discusses the use of factors other than default based on these criteria (Dourson et al., 1996).

The equation that EPA uses to determine the value of the RfC is:

$$RfC = NOAEL_{HEC} \text{ or } LOAEL_{HEC}(mg/m^3) \div (UF \times MF)$$

where:

$NOAEL_{HEC}$ = No Observed Adverse Effect Level or an equivalent value, such as a BMC, dosimetrically adjusted to an ambient human equivalent concentration
$LOAEL_{HEC}$ = Lowest Observed Adverse Effect Level, dosimetrically adjusted to an ambient human equivalent concentration
HEC = Human Equivalent Concentration
UF = Uncertainty Factor
MF = Modifying Factor.

The equation to develop a RfD is similar, where:

$$RfD = NOAEL \text{ or } LOAEL\ (mg/kg\text{-}day) \div (UF \times MF)$$

NOAEL = No Observed Adverse Effect Level or an equivalent value, such as a BMD
LOAEL = Lowest Observed Adverse Effect Level
UF = Uncertainty Factor
MF = Modifying Factor.

Finally, EPA provides a statement of confidence in their noncancer risk estimates (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA 1994). High confidence indicates a judgment that additional toxicity data are not likely to change the RfD/RfC. Low confidence indicates that at least a single, well-conducted, subchronic mammalian bioassay by the appropriate route is available. For such a minimum database, the likelihood that additional toxicity data may change the RfC is greater. Medium confidence indicates a judgment somewhere between high and low. Example of confidence statements for RfD/RfCs can be found on EPA's IRIS (U.S. EPA, 1999).

2.0 Hazard Identification

2.1 Review of Relevant Data Sources

TERA obtained a literature search in December 1998, and reviewed the availability of toxicological studies related to the lanthanides in combination and individually. Specifically, each individual lanthanide and some lanthanide-like elements were searched for the following elements: lanthanum (CASRN 7439-91-0), cerium (CASRN 7440-45-11), praseodymium (CASRN 7440-10-0), promethium (CASRN 7440-12-2), samarium (CASRN 7440-19-9), europium (CASRN 7440-53-1), gadolinium (CASRN 7440-54-2), terbium (CASRN 7440-27-9), dysprosium (CASRN 7440-91-6), holmium (CASRN 7440-60-0), erbium (CASRN 7440-52-0), thulium (CASRN 7440-30-4), ytterbium (CASRN 7440-64-4), lutetium (CASRN 7440-94-3), neodymium (CASRN 7440-00-8), yttrium (CASRN 7440-65-5), thorium (CASRN 7440-29-1) and scandium (CASRN 7440-20-2) and their respective salts. The HSDB and TSCATS databases were searched by the CASRN of the chemicals of interest and their appropriate salts.

All years of the MEDLINE and TOXLINE databases were searched (from when TOXLINE began in 1965 and MEDLINE began in 1966), using both CASRNs and name synonyms. The search strategy that we use for deriving RfDs/RfCs was employed in these databases. In MEDLINE, the appropriate MESH terms for the chemicals were used and metabolic and pharmacokinetic studies as well as toxicity studies and exposure studies were searched. In TOXLINE, CASRNs/synonyms were "ANDed" with an extensive list of search terms related to the oral and inhalation routes (e.g. nasal, ingest, etc.), some general health terms (e.g. chronic, neurotox, etc.) as well as an extensive list of reproductive developmental terms (e.g. fetal, sperm, etc.). The TOXLINE references from 1981-98 were downloaded in the search, using the chemical names/CASRNs in combination with our search strategy for finding health effects references.

In selecting studies to review, *TERA* first examined human or animal toxicity studies that evaluated the dose-response relationship between the chemicals of interest and potential health effects. Second, we considered studies on absorption, distribution, metabolism, excretion, or toxicokinetics, which would have an impact on the choice of appropriate uncertainty factors for the lanthanide RfDs and RfCs and the potential for route-to-route extrapolation for the development of a RfC from oral data if there was insufficient data from the inhalation data set. A variety of studies were found. These are summarized in Appendix Tables 1 and 2. We discussed the more relevant studies below for the purposes of establishing RfDs and RfCs .

2.2 Human Studies

Longerich et al. (1990) conducted an analysis of the drinking water of mothers of neural tube defect (NTD) infants and of normal infants for 14 selected trace elements. The tested elements included: Y, Ce, Mg, Cu, Zn, Sr, Mo, Cd, Sn, Sb, I, Ba, Pb and U. Twenty-eight NTD mothers and 28 control mothers of age-matched infants living in the same geographic area were included in the study. The drinking water of these mothers was collected and tested for the 14 trace elements by an inductively coupled plasma-mass spectrometry. The levels of Y (0.27±0.62

ug/L) and Ce (0.28±0.58 ug/L) in the drinking water of NTD mothers were higher than those in control groups (Y: 0.13±0.23 ug/L; Ce: 0.16±0.43 ug/L). However, the differences between the case group and the control were not statistically significant. Except Zn, all the other elements tested were found in higher, but not statistically significant, concentrations in the case group than in the control group. The result suggested a relationship of trace elements in drinking water with NTD, but a contribution of other factors to the NTD could not be excluded based on the available data. This study was limited by the limited exposure information.

Arsenault et al. (1996) investigated systemic gadolinium toxicity in patients with impaired renal function. One hundred fifty-one patients with a serum creatinine value ≥2.0 mg/dL during the 72-hour period immediately prior to a magnetic resonance imaging (MRI) examination were selected. These patients received gadolinium diethylenetriamine pentaacetic acid (DTPA) at dose of 0.1 mmol/kg as the contrast medium for the MRI examinations. A retrospective analysis was conducted of physician records, nursing records, radiology reports, laboratory data, and autopsy records during the 3 days before the MRI and for 30 days after the MRI. In addition, to assess any possible increase in mortality, 90-day mortality data from this group was compared to that in a control group of patients who had a MRI examination without using gadolinium DTPA as the contrast medium. Adverse events such as nausea (1.2%), rash (1.2%), seizure (0.6%) and headache (0.6%) were reported in patients received gadolinium DTPA, but the incidences were not significantly different from those in MRI patients with normal renal function in a previous study. Hematological and biochemical examinations showed no statistically significant change between pre-MRI and post-MRI examinations. A 14.6% mortality in the 90 days after MRI was found in gadolinium-exposed patients, but this value was comparable to that (13.8%) in the control group without exposure to gadolinium. Therefore, no significant adverse effect was observed after gadolinium DTPA exposure.

No studies were located on the effects in humans exposed to lanthanides via the inhalation route.

2.3 Inhalation Toxicity Data in Experimental Animals

BioResearch Labs Ltd. (1995) for Rhone-Poulenc Inc. reported a subchronic study on ceric oxide toxicity following inhalation exposure. Fifteen male and fifteen female Sprague Dawley CD rats were exposed by nose-only inhalation to CeO_2 aerosol at a concentration of 0, 5, 50, or 500 mg CeO_2/cu.m for 6 hours a day, 5 days a week for 13 weeks. This corresponded to a concentration of 0, 4.1, 41, or 407 mg Ce/cu.m. After adjustment for intermittent exposure, the exposures were to 0, 0.73, 7.3, or 73 mg Ce/cu.m. The mass median aerodynamic diameter (MMAD) was reported to be 2.00 microns, and the sigma g was 1.90 microns. Animals were examined daily for signs of toxicity, weekly for food consumption and body weight changes, and monthly for potential neurotoxic effects using a functional observation battery and motor activity testing. After 6 weeks of exposure and at study termination, hematology, clinical biochemistry, and urinalysis were performed. A gross pathological examination, assessment of organ weights, and a detailed histopathological evaluation were conducted at the end of the 13-week ceric oxide treatment. The histopathology examination included a thorough examination of the respiratory tract, including four levels of the nose.

The percentage of segmented (mature) neutrophils was significantly increased in high-concentration males; this parameter was also significantly increased in females at all concentrations, but the control group was unusually low, and the levels in exposed females were comparable to levels in control males. The toxicological significance of this effect is unclear. There was also a statistically significant increase in relative (but not absolute) spleen weight in males. Other significant effects due to ceric oxide exposure were confined to the respiratory tract. Concentration–related statistically significant increases in lung weight were seen in both male and female rats exposed to 50 and 500 mg/cu.m ceric oxide. The histopathological examination of the lung showed pigment accumulation at all exposure levels. We consider this pigment accumulation to be an indication of exposure, and not inherently adverse. Lymphoid hyperplasia in the bronchial lymph node was significantly increased in all exposed groups; the study authors considered this effect to be consistent with antigenic stimulation by the test material, and noted that this endpoint correlated with the volume of pigment. For the purpose of dosimetric conversions, we considered this endpoint to be a tracheobronchial effect, since the response is related to the dose to the bronchi. There was also a concentration-related incidence of larynx metaplasia that was statistically significant at mid and high concentrations. Alveolar epithelial hyperplasia was also statistically significant at mid and high concentrations in both sexes. For all of the respiratory tract endpoints, the low concentration was the NOAEL and mid concentration was the LOAEL. The corresponding NOAEL(HEC)s were 0.41 and 0.43 mg Ce/cu.m for alveolar epithelial hyperplasia in males and females, respectively, and 0.55 mg Ce/cu.m for increased lung weight in males and females. No NOAEL was identified for the bronchial lymph node hyperplasia; based on this minimal effect the LOAEL(HEC) is 0.85 or 0.82 mg Ce/cu.m in males and females, respectively. In the absence of data showing gender-specific differences, the LOAEL(HEC), based on the average of the tracheobronchial effects in both male and female rats, for the study is 0.83 mg Ce/cu.m (1.0 mg CeO_2/cu.m).

Abel and Talbot (1967) conducted a subchronic study on gadolinium oxide toxicity following inhalation exposure. Groups of six male and six female guinea pigs were exposed (whole body exposure) to 20 mg/cu.m Gd_2O_3 aerosol (particle sizes predominantly between MMAD of 0.1~1.0 µ) for 6 hours/day, 5 days/week for periods of 0, 40, 80, or 120 days. An equal number of animals exposed to atmosphere without gadolinium were used as controls. After exposure, the excised lungs were measured for compliance and lung tissues were evaluated histologically. As measured by an increase in the slope of the elastance curve, lungs exposed to Gd_2O_3 had less elastance than lungs from unexposed control guinea pigs. An increase in the duration of exposure produced a significant linear decrease in the lung elastance. In addition, 40-day exposure resulted in mild swelling and proliferation of septa cells and nodular lymphocytic hyperplasia. By 120 days after exposure, thickening of the alveolar wall, and numerous macrophages and nodular lymphocytic hyperplasia were observed in the lungs. The authors suggested the maximal permissible concentration should be less than 20 mg/cu.m of air. Limitations of this study include the use of only a single exposure concentration, the broad range of particle sizes in the exposure atmosphere, and the small number of animals per group. Since MMAD were not available in this study, and EPA (1994) does not provide default information for guinea pigs, no RDDR could be calculated. Thus, no HECs could be calculated.

Ball and van Gelder (1966) exposed mice (whole body exposure) to gadolinium oxide aerosol at an approximate concentration of 30 mg/cu.m of air for 6 hours/day, 5 days/week for 20

to 120 days, and monitored the surviving animals for the remaining duration of their lives. A total of 256 CFW mice, including both males and females, were used in the study, but the numbers of animals in each group were not given in the paper. The particle size was estimated to be between 0.1 and 0.5 micron diameter with a mean particle diameter of 0.312 ± 0.287 µ. Hematological examination was performed during the study on a randomized basis and at 12 and 18 months postexposure on surviving mice. Histopathology and necropsy procedures were also performed on mice that died during the exposure period, and on surviving mice at the time of death. There were no differences in hematology and weight gain between exposed and control mice up to and including 120 days of exposure. The histology indicates that gadolinium oxide is a low-grade pulmonary irritant that resulted in the localized accumulation of metal-containing microphages within the lung and a minimal interstitial thickening. In addition, gadolinium oxide exposed mice had an unusual histological finding of pulmonary calcification in the region of the alveolar basement region. The study demonstrates histopathological changes in the lung, but did not adequately characterize corresponding deficits in lung function. The authors did suggest that there is a trend, though not statistically significant, towards shortened life span in exposed mice. Limitations of this study also result from the use of only a single exposure concentration although a large number of animals was used.

2.4 Oral Toxicity Data in Experimental Animals

2.4.1 Acute Studies

Haley et al. (1961, 1963, 1964a,b, 1965, 1966) conducted a series of acute oral toxicity studies on the rare earth elements each in form of the chloride salt. The elements tested included gadolinium, samarium, terbium, thulium, ytterbium, praseodymium, neodymium, lutetium, europium, dysprosium, holmium, and erbium. For gadolinium and samarium, oral doses up to 2 g/kg were without lethality. Since it was impossible to obtain more concentrated solutions of these two compounds, no further tests of oral toxicity were conducted. The LD50 values for the other lanthanide elements were reported as: 5100 mg/kg for terbium chloride, 6250 mg/kg for thulium chloride, 6700 mg/kg for ytterbium, 4500 mg/kg praseodymium chloride, 5250 mg/kg for neodymium chloride, 5000 mg/kg for europium chloride, 7100 mg/kg for lutetium chloride, 7650 mg/kg for dysprosium chloride, 7200 mg/kg for holmium chloride, and 6200 for erbium chloride. The common symptoms of acute toxicity included writhing, ataxia, slightly labored and depressed respiration, arched back, stretching of limbs on walking, and lacrimation. Some deaths occurred within 24 hours, but the peak in deaths was not reached until 48 hours after the exposure.

2.4.2 Short Term Studies

Ogawa et al. (1992, 1994, and 1995) conducted a series of short term, subacute toxicity studies on several rare earth elements. The elements studied included lanthanum (La), yttrium (Y) and europium (Eu) in the form of hydrated chloride. In these studies, Wistar rats of both sexes received the compounds by gavage at doses of 0, 40, 200, or 1000 mg/kg for consecutive 28 days. Body weight and food consumption were monitored during the exposure, and hematological, serum-biochemical and complete histopathological examinations were performed

at the end of exposure. In addition, the concentrations of the rare earth elements in organs were determined.

Lanthanum was tested in Wistar rats (5 animals/dose/sex) at doses of 0, 40, 200, or 1000 mg/kg-day (as $LaCl_3 \cdot 7H_2O$) for 28 consecutive days, which corresponds to 0, 15.0, 74.8 or 374 mg La/kg-day (Ogawa et al. 1992). During lanthanum exposure, the body weight decreased (10-15% compared to control) in both sexes at the doses ≥ 74.8 mg La/kg-day, but they were comparable to that in the pair feeding group, suggesting a food consumption related body weight gain change. Hematological examination indicated that the percentage of eosinocytes in blood increased in females at doses ≥ 15.0 mg La/kg, and in males at doses ≥ 74.8 mg La/kg-day. The significance of this change is unknown. At doses ≥74.8 mg La/kg-day, a significant decrease of serum cholinesterase activity was observed only in females. The serum transaminase activity increased in both sexes at a dose of 374 mg La/kg. This finding was suggestive of hepatotoxicity, although there were no corresponding histopathological changes of the liver reported. The histopathological data indicated significant increases in lung granulation and giant cell appearance at doses ≥ 74.8 mg La/kg. As discussed in another paper (Ogawa et al. 1995), the author suggested that these changes in the lungs might be caused by the inhalation of the test compound. In addition, 374 mg La/kg resulted in stomach lesions, including infiltration in the submucosa in both sexes, erosion and dilatation of the acinus in males and swelling in the epithelium of females. Based on several of these changes, but primarily the body weight decrease, caused by La exposure, the LOAEL in this study was judged to be 74.8 mg La/kg-day and the NOAEL was judged to be 15.0 mg La/kg-day.

Yttrium was tested in Wistar rats (5 animals/dose/sex) at doses of 0, 40, 200, or 1000 mg/kg-day (as $YCl_3 \cdot 6H_2O$) for 28 consecutive days, which corresponds to 0, 11.7, 58.6, or 293 mg Y/kg-day (Ogawa et al. 1994). During yttrium exposure, decreased body weight compared to control occurred in males (25% lower) at the highest dose (293 mg Y/kg-day) and in females (10-15% lower) at doses ≥58.6 mg Y/kg-day. However, the decreases were comparable to that in pair feed controls, suggesting a food consumption related change. Hematological examination indicated that the percentage of eosinocytes in white blood cells increased in both males and females at doses ≥ 11.7 mg Y/kg. At doses ≥58.6 Y mg/kg-day, a significant decrease of the serum cholinesterase activity was observed only in females. In contrast to lanthanum exposure, no significant change in the serum transaminase activities was observed in yttrium exposed rats. The histopathological study indicated increases in lung granulation, giant cell appearance and eosinocyte infiltration in both sexes at doses ≥ 58.6 mg Y/kg-day, but the increases were dose independent and were not statistically significant from the control. Similar responses in the stomach following exposure to lanthanum were also observed following exposure to high dose of yttrium (293 mg Y/kg-day), including eosinocyte infiltration in submucosa in both sexes, and hyperkerotosis of forestomach and swelling epithelium of glandular stomach in females. Based primarily on the decreased body weight effect in female rats, the LOAEL in this study was judged to be 58.6 mg Y/kg-day and the NOAEL was judged to be 11.7 mg Y/kg-day.

Europium was tested in Wistar rats (10 animals/dose/sex) at doses of 0, 40, 200, or 1000 mg/kg-day (as $EuCl_3 \cdot 6H_2O$) for 28 consecutive days, which corresponds to 0, 16.6, 82.9, or 415 mg Eu/kg-day (Ogawa et al. 1995). Following europium exposure, decreased body weight (17%) compared to the control was only observed in females at the highest dose 415 mg Eu/kg-

day, while there was no difference in food consumption between the tested groups. No pair feeding control was included in this study. All the hematological changes observed were within the historical control data ranges in the testing laboratory. At doses ≥415 mg Eu/kg-day, a significant decrease of the serum cholinesterase activity was observed only in females. In contrast to lanthanum exposure, no significant change in the serum transaminase activities was observed in europium exposed rats. The histopathological study indicated dose independent increases in lung granulation, giant cell appearance and eosinocyte infiltration in both sexes. The authors suggested that these changes might be due to the inhalation of rare earth elements. Similar responses in the stomach following exposure to lanthanum were also observed following exposure to high dose of europium (415 mg Eu/kg-day), including hyperkeratosis of the forestomach and eosinocyte infiltration in the submucosa of both sexes. Based primarily on the decreased body weight in females and the stomach lesions in both sexes, the LOAEL in this study was 415 mg Eu/kg-day and the NOAEL was 82.9 mg Eu/kg-day.

2.4.3 Subchronic Studies

Haley et al. conducted a series of subchronic toxicity studies for rare earth elements each in the form of the chloride salt. The tested elements included gadolinium, samarium, terbium, thulium, ytterbium, praseodymium, neodymium, lutetium, europium, dysprosium, holmium, and erbium (Haley et al. 1961, 1963, 1964a,b, 1965, 1966). Groups of 6 rats/sex (CFN or CRW strain) received the test compounds in the form of chloride through diet at doses of 0, 0.01%, 0.1 %, or 1% of the diet for 12 weeks. Based on commonly used default values for body weights and food intake (0.05 kg food/kg body weight for rats), the corresponding doses were 0, 5, 50, and 500 mg/kg-day (of testing compound). During the exposure period, hematological changes, including erythrocytes, total leukocytes, differential cell count, platelets, hemoglobin, hematocrit, and body weight were examined periodically. At the end of the study, a complete histological examination was conducted.

Most of the tested rare earth chlorides had no effect on growth, hematology, and histopathology on exposed animals. Specifically for gadolinium exposure (Haley et al. 1961), the only significant exposure related changes were perinuclear vacuolization of the parenchymal cells of the liver and a coarse granularity of the their cytoplasm in male rats exposed to 500 mg/kg-day gadolinium chloride. Similar effects were not observed in females. For ytterbium chloride exposure (Haley et al. 1963), rats exposed to 500 mg/kg-day had gastric hemorrhages predominantly in the females (the number of animals responding was not reported). However, histopathological examination of these stomachs and of the esophagus revealed no tissue damage that would account for the gastric hemorrhages found at autopsy. An apparent dose dependent perinuclear vacuolization in the liver were observed in rats, mainly in males, exposed to terbium (≥5 mg/kg-day), thulium (50 mg/kg-day) and ytterbium (5 mg/kg-day) chlorides (control values were not provided, however). Since the observed perinuclear vacuolization of the liver cell is abnormal but the significance of this effect is not known and control values were not given, these changes should not necessarily be considered as an adverse effect caused by the exposure to rare earth elements. Based on the gastric hemorrhages in females, however, the LOAEL for ytterbium chloride was determined at 500 mg/kg-day, and the NOAEL would be 50 mg/kg-day. For the other tested rare earth compounds, gadolinium, samarium, terbium, thulium,

praseodymium, neodymium, lutetium, europium, dysprosium, holmium and erbium, equivocal, free standing NOAELs of 500 mg/kg-day were identified.

2.4.4 Chronic Studies

Schroeder and Mitchener (1971) fed yttrium nitrate at 5 ppm of the metal in drinking water to mice for up to 18 months. Groups of 54 CD mice of each sex were given yttrium nitrate in drinking water from weaning until natural death. Based on EPA default mouse water intake value of 0.19 L/kg-day (U.S. EPA, 1987), the calculated exposure dose was 0.95 mg Y/kg-day. Body weight was measured at monthly intervals up to 6 months, at 1 year and at 18 months of age. Dead animals were weighted and autopsied. Histopathological examinations were made on the heart, lung, liver, kidney, and spleen. Decreases in body weight were observed in males within first 6 months of exposure with 5% decreased at end of 6 months. In contrast, body weight decreases in females maintained in the whole exposure period with 17% decrease at the end of 18 months. However, survival curves were not affected following life long exposure. Yttrium was suggested to exert some carcinogenic activity, but the data were incomplete to definitively show this affect. No other toxicological end points were evaluated, making the adverse significance of the decreased body weight gain difficult to interpret. Additionally, the use of a single dose of yttrium does not allow for the development of a dose response curve and therefore the use of this data for risk assessment purposes is severely restricted.

Hutcheson et al. (1975) fed a diet that contained 10 heavy metals to CF-1 mice for three generations in this less-than-chronic study. Sixteen females and eight males were used in each dose group. All metals were fed in combination at 0, 1, 10, 100, and 1,000 times use-amount. For the lanthanides (as oxides) included in this diet, the use amount was (in ppm): dysprosium (1.2), europium (0.036), 1anthanum (0.40), samarium (0.80), scandium (0.12), terbium (1.20), ytterbium (0.12) and thulium (0.08). The mice were weighed periodically during the experiment. Hematological examinations of the blood sample from five 3-month-old dams in the 100-X group and control in each generation were conducted. In addition, gross necropsy observations were made on five adult third-generation mice from the 100-X group and five from the control group. There were no treatment effects reported among the treatment groups on survival, hematology, morphological development, maturation, reproduction or lactational performance. Although there were some significant differences in body weight between the tested groups, the differences were not consistent with levels of mineral added to the diet. Measurements of mineral content in carcasses from 100-X and control groups of the second-generation animals indicated a negligible gastrointestinal absorption of lanthanide compounds due to their poor solubility at tissue pH. These data provided a freestanding NOAEL for reproductive effects for each of the lanthanides listed above for up to 1000 times the use-amounts listed. Based on the EPA default values for food factor of 0.13 kg food/kg body weight (U.S. EPA, 1987), the calculated exposure doses of each lanthanide in the 1000-X group are: 156 mg Dy/kg-day, 5 mg Eu/kg-day, 52 mg La/kg-day, 104 mg Sm/kg-day, 16 mg Sc/kg-day, 156 mg Tb/kg-day, 16 mg Yb/kg-day, and 10 mg Tm/kg-day.

3. Dose Response Assessment

3.1 Toxicokinetics

Different forms of lanthanide may present different toxicity. There are three forms of lanthanide: soluble, insoluble and chelated compounds. The soluble salts include chloride or nitrate; insoluble compounds include oxide or hydroxide; and chelated compounds include citrate, diethylenetriaminepentaacetic acid (DTPA) or ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA) containing compounds. The toxicity of lanthanide after oral or inhalation exposure depends on its absorption, distribution, and its portal of entry effect.

Absorption of the form of a given lanthanide may determine its toxicity to the body. So far, all the available information on lanthanide absorption after oral exposure comes from studies on soluble lanthanide salts (see Appendix A, Table 2). No data on insoluble or chelated lanthanide absorption were identified. Therefore, a direct comparison of absorption rate between three forms of lanthanide could not be conducted. However, available data from soluble lanthanide indicate that DTPA (a well known chelator) treatment 1 or 2 days after oral administration of $CeCl_3$ (with milk) significantly decreased whole body retention of soluble cerium from 40% to 2% (Kostial et al. 1989). Whether the decreased cerium retention was caused by decrease in cerium absorption or by increase in its excretion is not known. However, these data suggested that different forms of lanthanide (soluble versus chelated for example) might lead to different systemic effects due to different bioavailabilities.

Different forms of lanthanides have different organ distribution and excretion rates once the portal of entry is bypassed and it is available systemically. Intravenous injected chelated lanthanide is transiently accumulated in the kidney and most of the injected dose is excreted in urine. Only small portion of the injected dose remained in other organs. In contrast, intravenous injected soluble salt is taken up by reticuloendothelial cells, and most of the dose is accumulated in the liver and spleen. As the result, intravenous injection of soluble lanthanide causes necrosis in the liver (Hirano and Suzuki 1996). Thus, different forms of lanthanide are expected to have a different systemic effect after it is absorbed into the body.

Toxicity data do not exist to judge which form of a given lanthanide is more toxic. For example, a three generation study (Hutcheson et al. 1975) on the toxicity of insoluble lanthanides, lanthanum and europium oxides, indicated that doses up to 52 mg La/kg or 4.7 mg Eu/kg mixed in the diet resulted in no consistent significant toxic effect in mice. Similarly, soluble lanthanum and europium, in the same dose range, had no adverse effect in 28-day studies when given by gavage (Ogawa et al. 1992, 1995). Nevertheless, a portal of entry effect did occur at the higher dose of soluble lanthanide gavage treatment, suggesting that the risk value for a specific route and method of administration should be derived from a toxicity study following the corresponding route or method of exposure.

Based on possible differences in absorption, distribution, and portal of entry effects, we recommended that the risk assessment of lanthanides should focus on specific forms to which the

toxicity data are available for deriving risk values. In the case of oral exposures, most of the available toxicity information comes from studies on soluble lanthanide. Therefore, a development of the RfD for soluble lanthanide is recommended. Inhalation risk assessment values should be conducted on chemicals with respiratory exposure and not be calculated from route-to-route extrapolations from other modes of administration.

3.2 Choice of Critical Studies

The available human data are not sufficient as a basis of either an RfC or an RfD.

The primary source of scientific uncertainty at this point in the development of the lanthanide RfC is the interpretation and paucity of the toxicological data, and the resulting implications for the choice of principal study and critical effect.

For ceric oxide, only one adequate toxicity study exists from which to determine an RfC: Bio-Research Labs (1995). We judged that bronchial lymph node hyperplasia was the critical effect, and that it is minimal at the lowest concentration. Thus, the $LOAEL_{[HEC]}$ for ceric oxide would be 1.0 mg/cu.m. (0.83 mg Ce/cu.m).

Of the two available inhalation studies for gadolinium oxide (i.e., Abel and Talbot, 1967; Ball and van Gelder, 1966), we consider the latter as a better basis for the development of an RfC. This is because toxicity was monitored over several exposure times and a large number of mice were used. Although only one concentration was evident from this study, the other study (Abel and Talbot 1967) gave some minimal support in another species. The critical effect of the Ball and van Gelder, (1966) study was calcification in the alveolar region and accumulation of macrophages in the lungs. The effect was not judged to be minimal. The resulting $LOAEL_{[HEC]}$ was 5.5 mg Gd_2O_3 (4.8 as mg Gd/cu.m.)

The oral data for subchronic or chronic exposure to lanthanides is likewise sparse and difficult to interpret for risk assessment purposes. The data of Ogawa (1992, 1994 and 1995) demonstrate dose-response effects for lanthanum, yttrium and europium as chlorides. The authors measured a number of parameters in pair-fed animals and determined both NOAELs and LOAELs. However, these studies were only for 28 days of exposure, which is shorter than the usually required length of study for development of an RfD. The Hutcheson et al. (1975) data provide multigenerational database testing of reproductive endpoints for the seven rare earth metals tested as oxides (i.e., dysprosium, europium, lanthanum, samarium, scandium, terbium, and thulium). These authors tested a series of doses (up to 1000-fold the normal use amount), but did not test high enough to demonstrate toxicity. The Schroeder and Mitchener (1971) study likewise did not test high enough doses to be used as a basis of an RfD. The Haley et al. data (1961, 1965, and 1966) provide additional subchronic dose response information on other rare earth elements as chlorides (gadolinium, samarium, dysprosium, europium, holmium and erbium). These authors tested for multiple endpoints and determined dose response for several parameters.

After reviewing all of this information, we recommend that the short term studies of Ogawa (1992, 1994 and 1995) be used to determine RfDs for the chlorides of lanthanum, yttrium and europium with corresponding NOAELs of 15.0, 11.7, and 82.9 mg/kg-day, respectively. The primary critical effect for each of these lanthanides is decrease body weight. Although these studies are only 28 days in duration, they measured portal of entry effects and established a dose-response. The other available subchronic data of Haley et al. (1961, 1965, and 1966) along with the multi-generation study of Hutcheson et al. (1975) can be used to support the derivation of these oral RfDs. The Hutcheson et al. (1975) study can also be used to derive preliminary RfDs for the oxides of dysprosium, europium, lanthanum, samarium, scandium, terbium, thulium, and ytterbium, however, only the derivations for lanthanum, europium, and scandium are presented here.

3.3 Choice of Uncertainty and Modifying Factors

The choice of uncertainty factors to be used with the appropriate critical effect of the various lanthanides depends on the areas of uncertainty that exist given the quality of the database. The available toxicity data for lanthanides in general necessitates the use of a larger composite uncertainty factors when compared to some other chemicals on EPA's IRIS (U.S. EPA, 1999). In addition, the toxicokinetic data on lanthanides are not sufficiently clear as to affect the value of individual uncertainty factors. The following discussion describes our choice of uncertainty factors for the determination of Reference Concentration (RfC) and Reference Dose (RfD) for the lanthanides. Table 1 summarizes these factors.

Human Variability (UF_H)

Do existing data account for sensitive individuals?

If yes, this suggests an uncertainty factor other than a default value of 10, as low as a value of 1 in some instances [see for example, the description of the uncertainty factor for nitrates on U.S. EPA's IRIS database (1999), where a NOAEL of a sensitive population was used as the basis of the RfD]. Scientists familiar with this area have considered this default factor to be composed of roughly equal parts for toxicodynamic and toxicokinetic differences among humans. Some recent work has attempted to quantify these distinctions (Renwick, 1993).

The available data in humans are insufficient to change the use of the default value of 10 for this area of scientific uncertainty for any RfDs or RfCs calculated here.

Inter-Species Variability (UF_A)

Do existing data allow for a quantifiable extrapolation of animal dose to the expected human equivalent dose for effects of similar magnitude? Or as is more likely the case, is a quantifiable extrapolation possible for NOAELs?

If yes, this suggests an uncertainty factor other than a default value of 10---with RfCs for example, a value of 3 is used when dosimetric adjustments are used in the determination of

Human Equivalent Concentration (HEC) [see U.S. EPA's IRIS (1999) for numerous examples]. Scientists familiar with this area have also considered this default factor to be composed of roughly equal parts for toxicodynamic and toxicokinetic differences between experimental animals and humans, but also recognize that some overlap with the uncertainty factor for intra-species variability exists. Some recent work has also attempted to quantify these distinctions in general (Renwick, 1993).

The RfCs for **ceric oxide** and **gadolinium oxide** should have an UF of 3-fold for this area of uncertainty, because dosimetric adjustments are used to extrapolate from animals to humans. This is standard practice within EPA (EPA, 1994).

Currently there are no dosimetric adjustments used in oral risk assessment values nor do sufficient toxicokinetic or toxicodynamic data exist to modify this area of uncertainty. Thus, the RfDs for the chlorides of **europium, lanthanum,** and **yttrium** would each have an uncertainty factor of 10-fold for this area. Likewise, a similar value would be applied to the oxides of europium, lanthanum and scandium. This is also standard practice within EPA (Dourson, 1994).

Subchronic-to-Chronic Extrapolation (UF_S)

Do existing data allow for a quantifiable extrapolation of the critical effect after subchronic exposure to the effect after chronic exposure? If different critical effects are identified after subchronic and chronic exposure, do they differ quantitatively?

U.S. EPA has occasionally used values less than 10 (nearly always 3-fold) with less than chronic exposures when data were available to support such a reduction [for example, see the RfD for arsine on U.S. EPA's IRIS (1999)]. Scientists familiar with this area also recognize that some overlap with this factor occurs with the database uncertainty factor (see following discussion).

The RfC for **ceric oxide** and **gadolinium oxide** would be expected to have an UF of 10-fold for this area of uncertainty because subchronic data was used to extrapolate to chronic exposure. Moreover, available toxicity data indicate an increasing severity in toxic response over duration to either of these chemicals. This increasing severity supports the use of the standard default value of 10-fold.

For the RfDs of the chlorides of **europium, lanthanum,** and **yttrium**, we also recommend the use of an UF of 10-fold. This is especially true for an RfD derivation that is predicated on an exposure period of something less than subchronic, in this case a 28-day study. The use of this short term study is supported somewhat, however, by the available information from multi-generation study which suggests no toxicity at lower doses and by the sub-chronic data reported by the Haley studies.

For the Hutchenson et al. (1975) study that is used to support the derivation of preliminary RfDs for the lanthanide oxides, an uncertainty factor of 10 would still be employed even in this three generation study. The parameters that were measured were conducted in animals that had exposure to the oxides for periods of time that were less than chronic and more

like sub-chronic intervals. There is no data that might justify using a factor less than the default value of 10.

LOAEL to NOAEL Extrapolation (UF_L)

Do existing data allow for the use of a NOAEL, rather than a LOAEL for the estimation of a RfD?

If a well-defined NOAEL does not exist, a factor of 10 is often used. However, U.S. EPA has often used values less than 10 (nearly always 3-fold) when data suggest that the LOAEL is for a minimally adverse effect, since the hypothesized NOAEL would likely be closer to this LOAEL then to a LOAEL with greater severity. For example, compare the RfDs for acrylonitrile and 1,2 epoxybutane on U.S. EPA's IRIS (U.S. EPA, 1999). The former RfD uses a 3-fold factor with degeneration and inflammation of nasal respiratory epithelium; the later RfD uses a 10-fold factor with more severe degenerative lesions of the epithelium.

The RfCs for both **ceric oxide** and **gadolinium oxide** have a LOAEL identified at the lowest concentration. For gadolinium oxide, the severity of response at the LOAEL (i.e., calcification in the alveolar region and accumulations of macrophages in the lung) suggests that the standard default uncertainty factor of 10-fold should be used for this area of uncertainty. However, we consider that the LOAEL for ceric oxide (i.e., bronchial lymph node hyperplasia) is minimal and should be reduced to a 3-fold factor.

For the chlorides of **europium, lanthanum,** and **yttrium** and the oxides of europium, lanthanum and scandium, an UF of 1-fold would be applied to the respective identified NOAELs for the RfD derivation.

Insufficient Database (UF_D)

Do existing data allow for a reasoned judgment of likely critical effect, given that any one toxicity study is unable to adequately address all possible outcomes?

If data exist from at least five studies (two chronic standard toxicity bioassays in different species, one two-generation reproductive bioassay and two developmental toxicity studies in different species), an uncertainty factor of 1 is applied. U.S. EPA has occasionally used values less than 10 (nearly always 3-fold) when data were available on several, but not all 5 studies [for example, see the RfD for acetaldehyde on U.S. EPA's IRIS (1999)], and factors of 10 (generally) when data were only available from a single study. Scientists familiar with this area also recognize that some overlap occurs with the subchronic to chronic uncertainty factor (discussed previously). The general solution to this problem when subchronic studies are available in two species, is to assign the uncertainty for lack of a chronic study to the subchronic to chronic factor, and not to the database factor.

The RfCs for **ceric oxide** and **gadolinium chloride** are based on the only studies identified that can be reasonably used to derive a risk assessment value. For ceric oxide, only one study is available in only one species. Thus, the standard default uncertainty factor of 10-

fold is considered reasonable. For gadolinium chloride, however, two bioassays in two different species are available. Although both of these studies are weak (from the point of view of an RfC derivation), they nonetheless are mutually supportive. Thus, the database is more than bare minimum and an intermediate factor of 3-fold factor is considered appropriate. This latter judgment is borderline, however, and might change with additional data.

The chlorides of **europium, lanthanum,** and **yttrium** have somewhat better than minimal data sets as compared to the RfCs. Each has information from two species and each has been tested in a multigeneration reproductive study, although the latter study was conducted with oxides of lanthanides and the principal studies on which the RfDs are based on the chloride salts. The usual 10-fold uncertainty factor for this area of uncertainty can be reduced. We suggest the use of a 3-fold factor.

Likewise, the uncertainty factor for the oxides of europium, lanthanum and scandium may be reduced from the default value of 10 to 3 if the data of the chloride salts are used to support the total data base. It has been previously argued that based on solubility, the chloride salts are likely to be more soluble and bioavailable than the oxide salts.

Modifying Factor (MF)

A modifying factor is not considered necessary with these chemicals. This is because the outstanding uncertainties can be adequately addressed with the standard factors. U.S. EPA only occasionally uses a modifying factor; for example, see the RfD for methyl ethyl ketone on U.S. EPA's IRIS (1999). The default value of 1 is appropriate for these lanthanides.

Composite Uncertainty and Modifying Factors

The composite uncertainty factor to use with a given database for developing RfDs and RfCs is a case-by-case judgment by experts, and should be flexible enough to account for each of the applicable five areas of uncertainty and any nuances in the available data that might change the magnitude of any factor. U.S. EPA describes its choice of composite UF and subcomponents for individual assessments on its IRIS database (U.S. EPA, 1999). The Table 1 discusses the recommended uncertainty factors for the various lanthanides:

Table 1. Various Lanthanides and Their Recommended Uncertainty Factors

Lanthanide	UF_H	UF_A	UF_S	UF_L	UF_D	MF	Total Factor
Ceric oxide (RfC)	10	3	10	3	10	1	3000[a]
Gadolinium oxide (RfC)	10	3	10	10	3	1	3000[a]
Europium chloride (RfD)	10	10	10	1	3	1	3000[b]
Lanthanum chloride (RfD)	10	10	10	1	3	1	3000[b]
Yttrium chloride (RfD)	10	10	10	1	3	1	3000[b]
Lanthanum oxide (preliminary RfD)	10	10	10	1	3	1	3000[b]
Europium oxide (preliminary RfD)	10	10	10	1	3	1	3000[b]
Scandium oxide (preliminary RfD)	10	10	10	1	3	1	3000[b]

[a] As a general default procedure, EPA combines four 10-fold factors to 3000. This includes consideration of several partial areas of uncertainty as well. Thus, three 10-fold factors and two 3-fold factors would also warrant a 3000-fold composite factor.

[b] As a general procedure in EPA, the data base uncertainty factor could be lower to 1-fold, if a credible argument is made that developmental toxicity, or other issues associated with the toxicity in younger animals, is not likely to be found based on an overall understanding of the chemical under study. We do not make this argument here, but are open to input.

3.4 Determination of RfD/RfCs

RfDs and RfCs are determined based on the choice of the most appropriate or most sensitive species, the choice of NOAEL, LOAEL or benchmark dose/concentration for the critical effect, and the judgment of the appropriate composite uncertainty factor. Usually, chemicals are looked at individually on the merits of their underlying toxicity data; occasionally, the toxicity of several chemicals are studied together, and data base gaps can be filled or enhanced by information from related chemicals.

Confidence in the estimated RfCs is considered low. For ceric oxide, only 1 adequate toxicity study exists from which to determine an RfC. Gadolinium oxide only has two available inhalation studies. Although toxicity was monitored over several exposure times for gadolinium oxide and a large number of animals was used, only one concentration was tested.

Confidence in the estimated RfDs for the lanthanide soluble salts is considered medium to low. This is because the oral data for subchronic or less-than-chronic exposure to lanthanides is somewhat less limited than that for the RfCs. For example, the data of Ogawa (1992, 1994 and 1995) which form the basis of RfDs for the chlorides of lanthanum, yttrium and europium demonstrate dose-response effects. The authors measured a number of parameters and determined both NOAELs and LOAELs. The brief length of these studies was offset in part by other work. Hutcheson et al. (1975) provided multigenerational testing of reproductive endpoints and additional supporting data of Haley et al. (1961, 1965, and 1966) also show no toxicity at lower doses. However, the Hutcheson et al. (1975) study reported limited reproductive data for the doses and a minimum of toxicological endpoints for only a single dose (100X). Therefore the confidence in the estimated RfDs for the oxides of lanthanides based on this study is considered low.

The resulting RfDs shown above are not necessarily internally consistent. For example, the RfD for Europium oxide is 2E-3 mg/kg-day, whereas the RfD for Europium chloride is 3E-2 mg/kg-day. This suggests that the oxide is more toxic than the chloride, whereas the toxicity of the soluble form of Europium would be expected to be greater than its oxide form. Unfortunately, the data supporting the development of these RfDs are not sufficiently strong to rule out such seeming inconsistencies.

We encourage the development of additional toxicity data in order to more confidently estimate RfDs and RfCs for these compounds. New data would be expected to raise the levels of these risk values for various lanthanides as shown in Table 2.

Table 2. Lanthanides and Their RfCs and RfDs

Lanthanide	Choice of Effect Level	UF	RfD/RfC
Ceric oxide as Ce/kg-day (RfC)	0.83 mg/cu.m (Bio-Research Labs, 1995)	3000	3E-4 mg/cu.m
Gadolinium as Gd/kg-day oxide (RfC)	4.8 mg/cu.m (Ball and van Gelder, 1966)	3000	2E-3 mg/cu.m
Europium oxide as Eu/kg-day (preliminary RfD)	5 mg/kg-day (Hutcheson et al., 1975)	3000	2E-3 mg/kg-day
Lanthanum oxide as La/kg-day (preliminary RfD)	52 mg/kg-day (Hutcheson et al., 1975)	3000	2E-2 mg/kg-day
Scandium oxide as Sc/kg-day (preliminary RfD)	16 mg/kg-day (Hutcheson et al., 1975)	3000	5E-3 mg/kg-day
Europium chloride as Eu/kg-day (RfD)	82.9 mg/kg-day (Ogawa et al., 1995)	3000	3E-2 mg/kg-day
Lanthanum chloride as La/kg-day (RfD)	15.0 mg/kg-day (Ogawa, 1992)	3000	5E-3 mg/kg-day
Yttrium chloride as Yt/kg-day (RfD)	11.7 mg/kg-day (Ogawa et al., 1994)	3000	4E-3 mg/kg-day

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Appendix A

Summary of Data

Appendix Table 1: Table of Toxicity Data for Rare Earth Elements

Appendix Table 2: Table of Pharmacokinetics Data for Rare Earth Elements

Appendix Table 1. Table of Toxicity Data for Rare Earth Elements

Acute toxicity - Summary									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Trace elements	Case-control study	Oral by drinking water	Human	Continuous with drinking water		28 /group	High levels of Y and Ce in the drinking water of neural tube defect (NTD) infants' mothers than that in control, but the difference is not statistically significant.	Twelve other trace elements were measured in addition to the lanthanide, and 13/14 tested elements were higher in case group. None of the differences were significant.	Longerich et al. 1990 (Canadian J. Appl Spec-troscopy)
Gadolinium	Retrospective analysis	Intravenous (i.v.)	Patients with renal insuffi-ciency (serum creatin-ine >2.0 mg/dL	Once	0.1 mmol/kg	151 patients	No significant changes in adverse effects, hematological values, and 90-day mortality.	Hematological values include: hemoglobin, hematocrit, platelet count, aspartate transaminase, bilirubin, alkaline phosphatase, calcium and phosphorus. Adverse effects include: nausea, rash, seizure and headache.	Arsenault et al. 1996 (Mayo Clin. Proc. 71: 1150-1154)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Yttrium chloride	Acute toxicity	Intratrach-eal instillation in 0.4 ml	Male rats	One dose	0, 10, 20, 50, 100, or 200 μg Y/rat	3 rats/group	≥10 μg/rat: increased b-glucuronidase, ≥20 μg/rat: increased LDH in BALF, ≥50 μg/rat: increased BAL protein, ≥100 μg/rat: increased AM and PMN in BALF.	Maximal increases in PMN, LDH, β-glucuronidase, and BAL protein was observed on day 1-2. Maximal increase of AM occurred on day 3. $t_{1/2}$ of Y in the lungs was 168 days. 40% of the initial dose still remained in the lungs after 162 days.	Hirano et al. 1990 (Toxicol. Appl. Pharmacol. 104:301-311)
Lanthanum chloride	Acute toxicity	Intratrach-eal instillation in 0.4 ml	Male rats	One dose	0, 0.5, 1, 10, 20, 50, 100 or 200 μg La/rat.	4 rats/group	≥1.0 μg/rat: increased LDH, β-glucuronidase, Ca, P in BALF, ≥50 μg/rat: increased protein, S and PMN in BALF, ≥100 μg/rat: increased AM in BALF, 200 μg/rat: increased BAL eosinophils.	The study also examined time course of the cellular and biochemical changes and La distribution in the lung and other organs. La half-life in the lung was 244 days.	Suzuki et al. 1992 (Toxicol. 76:141-152)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Gadolinium chloride	Acute toxicity	Intratrach-eal instillation in 0.4 ml saline	Male rats	One dose	0, 10, 20, 50 and 100 μg Gd/rat	4 rats/group	>= 10 μg/rat: increase LDH, and protein in BALF; >= 20 μg/rat: increase in epithelial lining fluid volume; >=50 μg/rat: increased PMN in BALF; 100 μg/rat: increased eosinophil in BALF.	The study also examined time course of the cellular and biochemical changes and Gd distribution in the lung. Gd half-life in the lung was 136 days.	Yoneda et al. 1995 (Fund. Appl. Toxicol. 28:65-70)
Rare earth nitrate	Acute toxicity	Oral by stomach tube in 50% water	Female rats	One dose	Not reported	30-35	LD50 mice (mg/kg): Didymium: 4100, Cerium: 4200, Praseodymium: 3500, Neodymium: 2750, Samarium: 2900, Europium: >5000, Gadolinium: >5000, Terbium: >5000, Dysprosium: 3100, Holmium: 3000, Ytterbium: 3100.	All chemicals tested are nitrates. Didymium nitrate contains 45-46% lanthanum, 32-33% neodymium, 9-10% praesodymium, 5-6% samarium, 3-4% gadolinium, etc.	Bruce et al. 1963 (Toxicol. Appl. Pharmacol. 5:750-759)
Cerium chloride	Acute toxicity	Intragastric gavage (i.g.) and subcutan-eous (s.c.) administra-tion.	Male mice	One dose		10/group	LD50 (i.g.)=1291 Ce/kg; LD50 (s.c.)=205 mg Ce/kg.		Stineman et al. 1978 (J. Environ. Pathol. Toxicol. 2:553-570)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Cerium chloride	Acute toxicity	Oral Intragastric gavage (i.g.) and subcutan-eous (s.c.) administra-tion.	Male mice	One dose	i.g. 1000 or 1163 mg Ce/kg; s.c. 136 or 173 mg Ce/kg.	10/group	**i.g. and s.c.:** hypertrophy, reticuloendothelial hyperplasia and hyperactive ymphoid follicles in the spleens after **i.g.** ≥1000 mg/kg caused gastritis and enteritis; **s.c.** ≥136 mg/kg caused focal midzonal necrosis in the livers.	The effect in spleen after i.g. and s.c. exposure was not explained clearly in the paper.	Stineman et al. 1978 (J. Environ. Pathol. Toxicol. 2:553-570)
Gadolinium and samarium chloride	Acute toxicity	Oral	Mice		Up to 2 g/kg		No lethality up to oral 2 g/kg. i.p. LD50 (mg/kg) gadolinium: 550, samarium: 585.	i.p. symptoms include decreased respiration, lethargy, abdominal cramps and diarrhea.	Haley et al. 1961 (Brit. J. Pharmacol. 17:526-532)
Dysprosium, holmium and erbium chlorides	Acute toxicity	Oral gavage or intraperiton-eal (i.p.) administra-tion	Mice			50-90 mice/study	LD50 (mg/kg) Dysprosium: 585 (i.p.) and 7650 (oral), Holmium: 560 (i.p.) and 7200 (oral), Erbium: 535 (i.p.) and 6200 (oral).	Symptoms: writhing, ataxia, slightly labored and depressed respiration, arched back, stretching of limbs on walking and lacrimation.	Haley et al. 1966 (Toxicol. Appl. Pharmacol. 8:37-43)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Rare earth nitrate	Acute toxicity	Intraperiton-eal administra-tion in water	Female rats	One dose	Not reported	30-40	LD50 mice (mg/kg): Didymium: 270, Cerium: 190, Praseodymium: 245, Neodymium: 270, Samarium: 285, Europium: 210, Gadolinium: 230, Terbium: 260, Dysprosium: 295, Holmium: 270, Erbium: 230, Thulium: 285, Ytterbium: 255, Lutetium: 335.	All chemicals tested are nitrates. Didymium nitrate contains 45-46% lanthanum, 32-33% neodymium, 9-10% praesodymium, 5-6% samarium, 3-4% gadolinium, etc.	Bruce et al. 1963 (Toxicol. Appl. Pharmacol. 5:750-759)
Rare earth nitrate	Acute toxicity	Intraperiton-eal administra-tion in water	Female mice	one dose	Not reported	35-55	LD50 mice (mg/kg): Didymium: 330, Lanthanum: 410, Cerium: 470, Praseodymium: 290, Neodymium: 270, Samarium: 315, Europium: 320, Gadolinium: 300, Terbium: 480, Dysprosium: 310, Holmium: 320, Erbium: 225, Thulium: 255, Ytterbium: 250, Lutetium: 290.	All chemicals tested are nitrates. Didymium nitrate contains 45-46% lanthanum, 32-33% neodymium, 9-10% praesodymium, 5-6% samarium, 3-4% gadolinium, etc.	Bruce et al. 1963 (Toxicol. Appl. Pharmacol. 5:750-759)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Rare earth nitrate	Acute toxicity	i.v.	Female rats	Single dose	Not reported	25-40	LD50 mice (mg/kg): Cerium: 1.3 (F) and 49.6 (M), Praseodymium: 7.4 ((F) and 77.2 (M), Neodymium: 6.4 (F) and 66.8 (M), Samarium: 8.9 (F) and 59.1 (M), Erbium: 35.8 (F) and 52.4 (M).	All chemicals tested are nitrates. Didymium nitrate contains 45-46% lanthanum, 32-33% neodymium, 9-10% praesodymium, 5-6% samarium, 3-4% gadolinium, etc.	Bruce et al. 1963 (Toxicol. Appl. Pharmacol. 5:750-759)
Cerium fluoride	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium concentrate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Moderately irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium carbonate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium chloride	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} < 5.0 g/kg Severe skin irritant;	100% mortality by day one.	Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Cerium nitrate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} , < 5.0 g/kg Mild primary skin irritant; Severely to moderately irritating to eyes	100% mortality by day two.	Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium acetate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg Non-primary skin irritant; Severely to moderately irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Yttrium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly and minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Yttrium nitrate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} < 5.0 g/kg Moderate primary skin irritant; Severely irritating to eyes	100% mortality by day three	Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Neodymium carbonate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Neodymium fluoride	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Neodymium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Lanthanum concentrate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Lanthanum oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly and minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Bastnasite concentrate	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Dysprosium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Erbium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly and minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Europium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Gadolinium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Mildly and minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)

Appendix Table 1 (continued)

Acute toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Praseodymium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Samarium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)
Cerium chloride	Acute toxicity	Oral Intragastric (i.g.) and by subcutaneous (s.c.)	Male mice	One dose	i.g. 1000 or 1163 mg Ce/kg; s.c. 136 or 173 mg Ce/kg.	10/group	No effect after i.g. exposure. s.c. 173 mg Ce/kg caused significantly depressed behavior at 4 hours after exposure.		Stineman et al. 1978 (J. Environ. Pathol. Toxicol. 2:553-570)
Terbium oxide	Acute toxicity	Gavage	Male and Female SD rats	Single Dose	5.0 g/kg (50% w/w in distilled water	5/sex	LD_{50} > 5.0 g/kg No signs of dermal irritation; Minimally irritating to eyes		Lambert et al., 1993 (J. Amer. Col. of Tox. 12:)

Appendix Table 1 (continued)

Subchronic toxicity – Summary									
Gadolinium oxide	Subchronic toxicity	Inhalation by aerosol	Mice	6 h/day, 5 days/week for 20-120 days	30 mg Gd_2O_3/cu.m.	20-30 mice/group/sex	≥1-2 week exposure increased mortality from pneumonia, ≥20-day exposure lead to a trend of decreased life span,	There was only one exposure dose.	Ball et al. 1966 (Arch Environ. Health 13:601-608)
Gadolinium oxide	Subchronic toxicity	Inhalation by aerosol, 92% or the mass was smaller than 0.563 ± 0.531 µm. Whole body exposure.	Guinea pigs	6 h/day, 5 days/week, for 40, 80, or 120 days	20 mg Gd_2O_3/cu.m.	6 animals/group/sex	Gd_2O_3 caused: less elastance in the lungs; alveolar cell hypertrophy, septal wall thickening, lymphoid hyperplasia and macrophage proliferation.	There was only one exposure dose.	Abel and Talbot 1967 (J. Pharmacol. Exp. Therap. 157:207-213)
Ceric oxide	Subchronic toxicity	Inhalation aerosol MMAD=2.0±1.9 µm, Nose only exposure.	Rats	6 h/day, 5 days/week for 13 weeks	0, 5, 50, or 500 mg CeO_2/cu-m.	15 rats/group/sex	≥ 5 mg/cu-m: pigment accumulation in nasal cavity, bronchi, trachea, and in the bronchial and other lymph nodes in both sexes; ≥ 50 mg/cu-m: alveolar hyperplasia in both sexes.	Examined: body weight, food consumption, neurotoxic effects, hematology, clinical biochemistry, urinalysis, complete histopathology. Besides the pathological observations, no other adverse effect was noted. Authors concluded that NOAEL was not established in this study.	Bio-Research Labs, 1995

Appendix Table 1 (continued)

Subchronic toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Lanthanum Chloride	Subacute toxicity	Oral gavage	Rats both sexes	Daily for 28 days	0, 40, 200 or 1000 mg $LaCl_3$ $7H_2O$/kg/day (0, 15.0, 74.8, or 374.0 mg La/kg)	4-5/group	**Body weight:** ≥200 mg/kg-day: decreased body weight gain. **Blood:** Increased blood eosinocyte in male rats at 40 mg/kg, and in both sexes at 200 mg/kg; increased serum transaminase activity in both sexes at 1000 mg/kg. **Lung:** Granulation and giant cell at ≥200 mg/kg in both sexes, **Glandular stomach:** 1000 mg/kg caused eosinophil infiltration in the submucosa in both sexes, erosion and dilatation of acinus in males, and swelling epithelium in females,	Small sample size Monitored: body weight, food consumption, and examinations on hematology, serum-biochemistry and histopathological examinations. La was accumulated in the liver, kidneys, spleen and femur in a dose-dependent manner with the highest accumulation in the liver.	Ogawa 1992 (Jpn J. Toxicol. Environ. Health 38:545-553)

Appendix Table 1 (continued)

Subchronic toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Yttrium Chloride	Subacute toxicity	Oral gavage	Rats both sexes	Daily for 28 days	0, 40, 200 or 1000 mg YCl_3 $6H_2O$/kg/day (0, 11.7, 58.6, or 293.1 mg Y/kg)	10 rats/group/sex	**Body weight:** decreased body weight gains in males at ≥200 mg/kg-day, and in females at 1000 mg/kg-day: **Blood:** Increased blood eosinocyte in both sexes at 40 mg/kg; **Lung:** No significant change; **Glandular stomach:** 1000 mg/kg caused hyperkeratosis in forestomach; the same dose also caused eosinophile infiltration in the submucosa in both sexes.	Small sample size. Monitored: body weight, food consumption, and examinations on hematology, serum-biochemistry and complete histopathological examinations. Y was accumulated in the kidney, femur, liver and spleen in dose-dependent manner with the highest accumulation in the kidney.	Ogawa 1994 (Jpn J. Toxicol. Environ. Health 40:374-382)

Appendix Table 1 (continued)

Subchronic toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Europium chloride	Subchronic toxicity	Oral gavage 5 ml of $EuCl_3 \cdot 6H_2O$ in 5% glucose solution.	Rats both sexes	Daily for 28 days	0, 40, 200 or 1000 mg $EuCl_3$ $6H_2O$/kg/day (0, 16.6, 82.9, or 414.7 mg Eu/kg/day)	10/group/sex	**Body weight:** ≥200 mg/kg-day: decreased body weight. **Blood:** At 1000 mg/kg-day, decreased mean cell hemoglobin, cell volume in both sexes, and decreases in WBC in recovery males, and in activated thromboplastin time in recovery females. **Lung:** Granulomatous lesions in 100% and 40% male rats at 40 and 200 mg/kg, and 60% females at 200 mg/kg. **Forestomach:** 1000 mg/kg caused basal cell hyperplasia and eosinophile infiltration in the submucosa in both sexes.	Authors concluded that the NOAEL is 200 mg/kg-day. Monitored: body weight, food consumption, and examinations on hematology, serum-biochemistry and histopathological examinations. Eu was accumulated in the liver, kidneys, spleen and femurs. The accumulation of Eu in these organs account for 1/100,000 of the total dose.	Ogawa et al. 1995 (J. Environ. Pathol. Toxicol. Oncol. 14: 1-9)

Appendix Table 1 (continued)

Subchronic toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Gadolinium and samarium chloride	Subchronic toxicity	Oral by diet	Rats	12 weeks	0, 0.01, 0.1, or 1% in diet (5, 50 and 500 mg/kg-day)	6 rats/group/sex	1% Gadolinium chloride resulted in perinuclear vacuolization of the parenchymal cells of the liver and a coarse granularity of their cytoplasm in male rats. No effect after exposure to samarium chloride.	Examined: hematology, growth rate, complete histopathology.	Haley et al. 1961 (Brit. J. Pharmacol. 17:526-532)
Europium chloride	Subchronic toxicity	Oral by diet	Rats	12 weeks	0, 0.01, 0.1, or 1% in diet (5, 50 and 500 mg/kg-day)	6 rats/group/sex	No effect in terms of growth, histopathology and hematology.		Haley et al. 1965 (J. Pharmaceut. Sci. 54:643-645)
Dysprosium, holmium and erbium chlorides	Subchronic toxicity	Oral by diet	Rats	12 weeks	0, 0.01, 0.1, or 1% in diet (5, 50 and 500 mg/kg-day)	6 rats/group/sex	No effect in terms of growth, histopathology and hematology.	Examined: hematology, growth rate, and complete histopathology except the stomach.	Haley et al. 1966 (Toxicol. Appl. Pharmacol. 8:37-43)

Appendix Table 1 (continued)

Subchronic toxicity – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Yttrium nitrate	Chronic toxicity	Oral in drinking water	Mice	From weaning until natural death	5 ppm Y (mg/L) in drinking water (1mg/kg-day, based on default mouse water intake 0.19 L/kg-day)	54 mice/sex	Decreased growth and body weights were observed in 12 out of 16 time intervals. Survival curve of yttrium did not differ from those of the control group, however, males fed yttrium lived even longer than their controls. Yttrium is somewhat tumorigenic and carcinogenic, although the data were not statistically significant.		Schroeder and Mitchener 1971 (J. Nutr. 101:1431-1438)

Appendix Table 1 (continued)

Reproductive and Developmental toxicity - Summary									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Cerium chloride	Develop-mental toxicity	Intrascapu-lar subcu-taneous. Dissolved in Na citrate 1:3	Female mice	On 7, or 12 of gestation or on day 2 after parturition	80 mg Ce/kg	10-22 mice/group	1. in utero Ce exposure on day 12 and mother Ce exposure on lactation day 2 decrease offspring body weight; 2. in utero Ce exposure decreases pups retrieval time; 3. in utero Ce exposure increases frequency of rearings.	Body weight conclusion was not supported by provided data.	D'Agostino et al. 1982. (J. Toxicol. Environ. Health 10:449-458)
Rare earth oxides	Development al toxocity	Oral by diet	Female mice	3 generations	Each dose contained 0, 1, 10, 100, or 1000x the amount of chemicals listed below: La 0.40 ppm (0.052 mg/kg-d) Sm 0.80 ppm (0.104 mg/kg-d) Eu 0.036 ppm (0.005 mg/kg-d) Tb 1.20 ppm (0.156 mg/kg-d) Dy 1.20 ppm (0.156 mg/kg-d) Tm 0.08 ppm (0.010 mg/kg-d) Yb 0.12 ppm (0.016 mg/kg-d)	16 females/group	Different groups showed different growth rats during different generations. No other significant changes were observed.	The examinations included: mortality, morbidity, survival rate, growth rate, hematology, morphological development, maturation, reproduction, and lactational performance.	Hutcheson et al. 1975 (J. Nutr. 105:670-675)

Appendix Table 2. Table of Pharmacokinetics Data for Rare Earth Elements

Pharmacokinetics - Summary									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Cerium Hydroxide	Acute	Inhalation, Aerosol (1.4 µm ± 2.0)	Rats	Inhalation 10 min.	3.0 or 170 µCi/kg (0.45 or 175 µCi/L)	34 rats either sexes	Skeleton $T_{1/2}$=230 days. Lung $T_{1/2}$=2 130 days.	Skeletal accumulation as high as 66% of whole body burden. Liver could be 44%. Lung could be 30%. The maximal accumulation in these organs does not present at the same time	Thomas et al. 1972 (Radiat. Res. 49:580-610)
Cerium chloride	Acute	Nose-only inhalation Aerosol (MMAD= 0.83 µm ± 1.7)	Hamsters	Once for 20 min.	4.2 µCi/L	40 hamsters	Day 2: 50% ^{144}Ce was associated with the lung, 7% with the liver and skeleton. The rest with pelt and GI tract.		Sturbaum et al. 1970 (Radiat. Res. 44:359-367)
Ytterbium Oxide	Acute	Intratracheal instillation	Female rats	One dose	0.026 µg YbO_3	4-5 rats/group	Lung clearance $T_{1/2}$ = 21 days. Whole body clearance = 22 day.	The highest body burden is on day 0.042 and has 11% dose. Chemical form in the body is unknown.	Rhoads and Sanders 1985 (Environ. Res. 36:359-378)
Cerium chloride	Acute	Oral gavage	0-6 or 6-24 h old mice or rats, 6-24 h old piglets	One dose	1 µCi (^{141}Ce-^{144}Pr chloride or ^{141}Ce-^{144}Pr citrate) for mice or rats, 200 µCi ^{141}Ce-^{144}Pr chloride for piglets	20 mice/group, 7-12 rats/group, 1-4 pigs/group.	Absorption (0-21 days): 31% in 0-6 h old mice, 24% in 6-24 h mice, 13% in 6-24 h rats, 10% in 6-24 h piglets,	Skeleton accumulates the most followed by the liver. Absorption =body retention – GI tract	Eisele et al. 1980 (Health Physics 39:185-192)

Appendix Table 2 (continued)

Pharmacokinetics – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Cerium nitrate	Acute	Oral by gavage	Male rats	One dose	10^5 cpm/rat	5-7 rats/group fed or fasted.	Fasted rats have more whole body retention on day 6 (0.15%) than fed rats (0.03%), but not before day 3. Milk increased retention in day 1 (53.9%) than grain (3.6%).		Sagan et al. 1973 (Radiat. Res. 53:480-487)
Cerium chloride	Acute	Oral as $^{144}CeCl_3$ with food	Miniature swine	Once	Not reported	4 animals	In 10 days, 0.001% ^{144}Ce was excreted in urine, <0.01% present as body burden.	Authors concluded that absorption was <0.01%.	McClellan et al. 1965 (Aerosp. Med. 36:16-20)
Cerium chloride	Acute	Oral in milk	6-day old rats	Take milk for 8 h	6.7 MBq ^{141}Ce/kg bw, Zn-DTPA is given on day 1-2 or day 2-3.	10-12 rats/group	Control whole body retention is 40.19%. DTPA on day 1-2 results in retention of 2.03%. DTPA on day 2-3 results in retention of 1.89%	Chelate decreases Ce retention, but the mechanism is unknown. It could be: decrease in absorption in GI tract, or increased absorption and excretion in urine.	Kostial et al. 1989 (Biol. Trace. Elem. Res. 21:213-218)
Cerium chloride	Acute	Oral as $^{141}CeCl_3$ with milk, food or food ingredients	6-day old Rats	8 h in milk, food or food ingredients	0.026 mg Ce with 4 uCi ^{141}Ce (specific activity = 0.15 mCi/mg Ce)	6 rats/group	Whole body retention in rats fed with milk is 3x activity in rats fed with food, and 7.5x activity in rats fed with ingredients.	92%-98% activity is in gut. Main difference comes from gut activity. Internal organs have 2-2.8 fold difference.	Kostial et al. 1987 (Int. J. Radiat. Biol. 51:139-145)

Appendix Table 2 (continued)

Pharmacokinetics – Summary Continued									
Chemical Name	Study Type	Route	Species	Duration	Exposure levels	Number	Response	Comments	Reference
Promethium	Acute	Oral. ^{147}Pm, chemical form not reported	Rats	One gavage	3.5 µCi/neonatal, 10.7 µ/Ci /adult	8-9 rats/group	Day 7-9 after gavage: total absorption rate is 5.4% in neonatal and 0.007% in adult.		Sullivan et al. 1984 (Environ. Res. 35:439-453)
Promethium	Acute	Oral ^{147}Pm, chemical form not reported	Swine	One gavage	6.5 µCi/animal	5-9 swine/group	Day 5-9 after gavage: total retention is 1.77% in neonatal and 3.4% in adult.		Sullivan et al. 1984 (Environ. Res. 35:439-453)
Promethium chloride	Acute	Oral by gavage	Rats	One dose	10 µCi/rat	8 fed rats and 6 fasted rats	Over 7 days, total absorption is 0.013% in fed rats (most in the carcass) and 0.072% in fasted rats (most in the liver).		Sullivan et al. 1986 (Health Physics 50:223-232)
Yttrium Chloride	Subacute toxicity	Oral by gavage	Rats both sexes	Daily for 28 days	0, 40, 200 or 1000 mg YCl_3 $6H_2O$/kg/day	10 rats/group/sex	Total accumulation of Y in rats was about 50 times as much as that of La. The highest accumulation of Y was found in the kidney.	Monitored: body weight, food consumption, and examinations on hematology, serum-biochemistry and complete histopathological examinations.	Ogawa 1994 (Jpn J. Toxicol. Environ. Health 40:374-382)

Appendix B

Calculations for Various Human Equivalent Concentrations

BioResearch Labs Ltd. (1995):

The exposure concentrations were 5, 50, or 500 mg CeO_2/cu.m (0, 4.1, 41, or 407 Ce/cu.m) for 6 h/day, 5 days/week. Particle size, MMAD, was reported to be 2.00 microns, and the sigma g was 1.90 microns. Based on EPA's default Sprague Dawley rat body weight for subchronic assay, 0.267 kg for male and 0.204 kg for female, RDDRs were calculated and listed in the following table. In addition, the table also includes all the calculation results for HECs. The concentration unit listed is mg Ce/cu.m.

Effect	NOAEL	NOAEL(adj)	LOAEL	LOAEL (adj)	RDDR	NOAEL(HEC)
PU-M	4.1	0.73	41	7.3	0.564	0.41
PU-F	4.1	0.73	41	7.3	0.588	0.43
TH-M	4.1	0.73	41	7.3	0.755	0.55
TH-F	4.1	0.73	41	7.3	0.76	0.55
TB-M			4.1	0.73	1.167	0.85 (LOAEL)
TB-F			4.1	0.73	1.122	0.82 (LOAEL)

NOAEL (adj) = NOAEL x 6/24 x 5/7
LOAEL (adj) = LOAEL x 6/24 x 5/7
NOAEL (HEC) = NOAEL (adj) x RDDR
LOAEL (adj) = LOAEL (adj) x RDDR

Abel and Talbot (1967):

The exposure concentration was 20 mg Gd_2O_3/cu.m for 6 h/day, 5 days/week. Particle size ranged from 0.1 to 1.0 micron with 92% of the mass smaller than 0.563 ± 0.531 micron. Based on particle size information, it is assumed that 0% mass is at size ≤ 0.1 micron and 92% mass is ≤ 0.563 micron. By using two points, (0.1, 0%) and (0.563, 92%) to make a log-probability line, the expected 50% mass was calculated at 0.2558 micron; 84.1% of the mass was at 0.4853 micron, and 15.9% at 0.1348 micron. Thus, the MMAD was 0.2558 micron. The log concentration difference between either 84.1% and 50% mass or 50% and 15.9% mass is 0.2781. Thus sigma g is 10^x(0.2781), or 1.8971. Since the MMAD < 0.5 micron and guinea pig data were used, the RDDR could not be determined based on the RDDR software (EPA RfC guideline 1994) or the rat RDDR table (EPA RfC guideline 1990). Because the RDDR could not be determined, HECs could not be calculated.

Ball and van Gelder (1966):

The exposure concentration was 30 mg Gd_2O_3/cu.m for 6 h/day, 5 days/week. Particle size was ≥ 0.1 micron with 70% of the mass smaller than 1.0 micron. By using two points, (0.1, 0%) and (1.0, 70%), to make a log-probability line, the expected 50% mass was calculated at 0.5179 micron and 15.9% at 0.1687 micron. Thus the MMAD was 0.5179 micron. The log difference between 15.9% and 50% is 0.4872. Thus, the sigma g is 10^x(0.4872) or 3.07.

Mouse body weights were calculated based on EPA default values for subchronic assay in BAF1 and B6C3F1 mice, which resulted in 0.0269 kg for male mice and 0.0225 kg for female mice. By using the RDDR software (EPA RfC guideline 1994), the RDDR for the thoracic region was calculated:
RDDR (TH) = 1.191 for male and 1.041 for female. The following HEC was then derived.

LOAEL = 30 mg Gd_2O_3/cu.m
LOAEL (adj) = 30 x 6/24 x 5/7 = 5.36 mg Gd_2O_3/cu.m
LOAEL (HEC) = 5.36 x 1.191 = 6.38 mg Gd_2O_3/cu.m (males) or 5.36 x 1.041 = 5.58 mg Gd_2O_3/cu.m (females).

The corresponding LOAEL (HEC) in mg Gd/cu.m = 5.53 for males or 4.84 for females.

Appendix C

Mixtures Risk Assessment for the Lanthanides

Introduction:

Conducting environmental risk assessments very often requires evaluating the significance of exposures to chemical mixtures. In 1986, the U.S. Environmental Protection Agency's Risk Assessment Forum (RAF) published *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986). This was followed by a Technical Support Document on Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1990). These guidelines represent the current Agency's science policy on chemical mixtures and serve as procedural guides.

However, because the science in the area of mixtures risk assessment continues to evolve, EPA has continued to evolve its guidelines. Recently, a document developed by EPA entitled "Guidance for Conducting Health Risk Assessment of Chemical Mixtures" was reviewed by experts in toxicology, mechanistic and pharmacokinetic modeling, statistics, and risk assessment (EPA, 1999).

The experts agreed that a tiered approach to risk assessment is a good idea, similar to what EPA uses in its current guidelines. This approach should be supported by a tiered approach to mixture toxicity testing, noting a need to look at multiple endpoints and screening assays.

For noncancer toxicity, the reviewers agreed that the hazard index (HI) is an acceptable default method to handle risk characterization of mixtures of chemicals for which dose additivity of components is considered appropriate. Here, "appropriate" requires that the components act by the same mechanism and do not interact with each other. If enough data are not available to know for sure whether the components act by the same mechanism, acting on the same target organ will suffice. Several other approaches, such as a Weight-of-Evidence (WOE) interactions index, were discussed and were considered as useful as the HI.

Any risk assessment should outline the assumptions and criteria associated with the model choice and then describe how well the particular mixture or situation being assessed agrees with that choice. The extent to which the model is not a perfect match should also be described at least qualitatively, if not quantitatively.

Toxicity of Lanthanides:

As discussed above for the lanthanides, the available human data are not sufficient as a basis for the development of either an RfC or an RfD. Moreover, the available animal toxicity data are limited to only a few studies for each of the several lanthanides, and even fewer studies from which to estimate various risk values (see section 3.2, Choice of Critical Studies).

For example, ceric oxide has only one adequate toxicity study from which to determine an RfC. The critical effect is limited to the respiratory system. For gadolinium oxide, Ball and van

Gelder (1966) also show toxicity in the lung as the critical effect. The resulting RfCs for these two chemicals are 3-fold apart.

The oral toxicity data used to determine the RfDs for the lanthanides are likewise sparse and difficult to interpret. For example, the data of Ogawa (1992, 1994 and 1995) demonstrate dose-response effects for chlorides of lanthanum, yttrium and europium. The authors measured a number of parameters in pair-fed animals and determined both NOAELs and LOAELs. Decreases in body weight and stomach lesions appeared to be the critical effect for each of these lanthanides. Although, these studies were only for 28 days of exposure, which is shorter than the usually required length of study for development of an RfD, they measured portal of entry effects and established a dose-response. The other available subchronic data of Haley et al. (1961, 1965, and 1966) along with the multigeneration study of Hutcheson et al. (1975) supports the critical effects found and the derivation of these oral RfDs. The resulting RfDs for these 3 lanthanides lie within a range of 7-fold of each other.

Preliminary RfDs were also developed for oxides of europium, lanthanum and scandium based on the study of Hutcheson et al. (1975). Numerous difficulties exist with the interpretation of this study making the resulting RfDs only preliminary in nature. Values for these RfDs lie within 10-fold of each other.

Mixtures Risk Assessment:

Several options exist to conduct risk assessments for the mixture of lanthanides found at the Mountain Pass mine site. First, mixtures of specific lanthanides could be tested for toxicity. Studies of 90 days duration would be ideal, but studies of shorter duration would still be helpful. The RfDs for chorides of lanthanum, yttrium, and europium, for example, are based on 28-day studies (as above). Such testing is essentially Tier 1 of EPA's (1986) chemical mixtures guidelines and draft update (U.S. EPA, 1999).

A second option would be to base a risk assessment for any particular mixture of lanthanides on a sufficiently similar mixture. This approach is basically Tier 2 of EPA's (1986) guidelines and draft update (U.S. EPA, 1999). Unfortunately, no mixture of lanthanides has been tested as evidenced in the appendix tables to this document.

A third option would be to base a risk assessment for any particular mixture of lanthanides on the toxicity of individual lanthanides. This approach is basically Tier 3 of EPA's (1986) guidelines and draft update (U.S. EPA, 1999). RfCs (for cerium and gadolinium) and RfDs (for chlorides of lanthanum, yttrium and europium and oxides of europium, lanthanum and scandium) exist for the lanthanides as developed in this document. The use of these values to determine the likely Hazard Index for mixtures of these specific lanthanides is supported and recommended by EPA (1986) guidelines.

However, it may be that several lanthanides exist in the mixture that do not have an RfD or RfC value. In such cases, the risk assessment scientist must make a judgment regarding whether the existing RfCs and RfDs might be useful as a surrogate for the missing information. Based on possible differences in absorption, distribution, and portal of entry effects, we recommended that

this judgment focus on specific forms to which the toxicity data are available for deriving risk values. In the case of oral exposures, most of the available toxicity information comes from studies on soluble lanthanide. Therefore, development of RfDs for different soluble lanthanides based on the existing soluble RfDs calculated in this text seems appropriate. Likewise, development of RfDs for different insoluble forms, based on preliminary insoluble RfDs calculated in this text seems appropriate. Similarly, the development of RfCs for different less-soluble lanthanides based on the existing RfCs calculated in this text also seems appropriate. For soluble forms, however, such development of RfCs may not be appropriate.

Regardless of how these judgments are made, the risk assessor should proceed with caution. At the very least, one should find any comparative toxicity or toxicokinetic data on the compounds to be compared. For example, one can look in the appendix to determine the similarities (or differences) in the acute toxicity data of different lanthanides in the mixture. (In general, the acute toxicities of this class of chemicals are similar.) Afterwards, a judgment based on sufficient similarity should be carefully described, noting appropriate caveats.

References:

U.S. EPA. 1986. Guidance for Conducting Health Risk Assessment of Chemical Mixtures. 51 FR 34014. September 24.

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