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Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Soluble Lutetium (CASRN 7439-94-3)

U.S. EPA Office of Research and Development
National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (Cincinnati, OH)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

[1]Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR LUTETIUM (CASRN 7439-94-3)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by at least two National Center for Environment Assessment (NCEA) scientists and an independent external peer review by at least three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

PPRTV assessments are eligible to be updated on a 5-year cycle to incorporate new data or methodologies that might impact the toxicity values or characterization of potential for adverse human-health effects and are revised as appropriate. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. Environmental Protection Agency (EPA) Superfund and Technology Liaison (https://www.epa.gov/research/fact-sheets-regional-science).

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Lutetium (Lu), CASRN 7439-94-3, a member of the lanthanide series, is a metallic element with an atomic number of 71. One of the few commercial uses of lutetium is as a catalyst in cracking, alkylation, hydrogenation, and polymerization processes (Bunzli, 2013; Lewis and Hawley, 2007). Radioactive lutetium (Lu-177) has been used in radiopharmaceuticals (Banerjee et al., 2015). Occupational and public safety health risks associated with exposure to rare earth metals like lutetium may occur during mining, transportation, processing, commercial use, and waste disposal (TaekRim et al., 2013). Lutetium is listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2018b); however, it is not registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018).

Lutetium occurs naturally in the earth's crust at a concentration of approximately 0.8 ppm (Bunzli, 2013). Lanthanides like lutetium are typically found as trivalent cations in insoluble compounds within rock-forming minerals such as carbonates, oxides, phosphates, and silicates (USGS, 2016). Lutetium occurs at a concentration of 0.003% in the mineral monazite, which is the element's commercial source. Monazite is digested using caustic soda to obtain the lanthanides as hydroxides. The hydroxides are then treated with hydrochloric or nitric acid to remove thorium and other elements, and further processed to recover the individual lanthanides (Bunzli, 2013).

Lutetium is a soft, ductile, silvery-white metal that is difficult to isolate. It is relatively stable in air, reacts slowly with water, and is soluble in dilute acid (Haynes, 2014; Lewis and Hawley, 2007). Table 1 summarizes the physicochemical properties of lutetium and two of its commonly occurring soluble salts. Like other lanthanides, lutetium forms mostly ionic compounds, has a high affinity to oxygen, and exists in its +3 oxidation state in compounds or in solution under most conditions. In general, lanthanide salts of chloride, nitrate, and perchlorate are soluble, while compounds of hydroxide, carbonate, phosphate, and fluoride are insoluble (Evans, 1990).

Table 1. Physicochemical Properties of Lutetium and Soluble Salts

Property (unit)	Lutetium	Lutetium Chloride	Lutetium Nitrate
CASRN	7439-94-3	10099-66-8	10099-67-9
Formula	Lu	$LuCl_3$	$Lu(NO_3)_3$
Physical state	Solid	Solid	Solid
Boiling point (°C)	3,402[a]	>750 (sublimes)[b]	NV
Melting point (°C)	1,663[a]	925[a]	NV
Density (g/cm^3 at 25°C)	9.84[a]	3.98[a]	NV
pH at which precipitation starts (0.1 M $Lu[NO_3]_3$)	5.74 (ion)[c]	NV	NV
Vapor pressure (mm Hg at 25°C)	NA	NA	NA
Solubility in water (mg/L at 25°C)	NV	Soluble[a]	Soluble[a]
Atomic or formula weight (g/mol)	174.967[a]	281.326[a]	360.982[a]
Flash point (closed cup in °C)	NA	NV	NV

[a]Haynes (2014).
[b]O'Neil (2013).
[c]Bunzli (2013).

NA = not applicable; NV = not available.

Lutetium chloride ($LuCl_3$), CASRN 10099-66-8, is a hygroscopic, white, monoclinic crystalline solid that is water soluble (Haynes, 2014). Lutetium chloride is used in laser crystals and optical fibers and as an optical dopant (Metall Rare Earth, 2015). Lutetium chloride also exists as the hexahydrate ($LuCl_3 \cdot 6H_2O$; CASRN 15230-79-2) and the radiolabeled ($^{177}LuCl_3$; CASRN 16434-14-3) forms. Lutetium nitrate ($Lu[NO_3]_3$), CASRN 10099-67-9, is a soluble, hygroscopic, colorless solid (Haynes, 2014). Soluble lutetium salts (e.g., chloride and nitrate), once dissolved in aqueous solution or biological systems, would rapidly form Lu^{3+} ions with bound water molecules. The solubility of Lu^{3+} in aqueous solution is pH dependent. At pH below approximately 5.7, the Lu^{3+} ion is bound to water molecules as its soluble aqua ion ($Lu[H_2O]_6^{3+}$), which would be the predominant lutetium species found in the stomach (pH 1−2). Above pH 5.7, as would be found in the small intestines and blood, lutetium will begin to precipitate out of solution as the bound water molecules are converted to hydroxide ions ($Lu[OH]_3[H_2O]_3$). In biological systems, Lu^{3+} ions may also bind to other oxygen donor molecules, such as carboxylic acids (proteins) and phosphates (nucleic acids) (Evans, 1990).

A summary of available toxicity values for lutetium and lutetium compounds from U.S. EPA and other agencies/organizations is provided in Table 2. A 2007 PPRTV assessment from the U.S. EPA was previously available for "Stable Lutetium." The assessment herein provides an updated evaluation of soluble lutetium based on recent scientific literature and current PPRTV assessment practices.

Table 2. Summary of Available Toxicity Values for Lutetium (CASRN 7439-94-3) and Lutetium Compounds

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012)
ATSDR	NV	NA	ATSDR (2018)
IPCS	NV	NA	IPCS (2018); WHO (2018)
CalEPA	NV	NA	CalEPA (2016); CalEPA (2018a); CalEPA (2018b)
OSHA	NV	NA	OSHA (2017a); OSHA (2017b)
NIOSH	NV	NA	NIOSH (2016)
ACGIH	NV	NA	ACGIH (2018)
DOE (PAC)	PAC-3: 2,000 mg/m^3; PAC-2: 330 mg/m^3; PAC-1: 30 mg/m^3 (for lutetium and lutetium oxide)	PAC-3 and PAC-2 based on adjustments to 1-hr TEELs; documentation of the basis for TEEL values was not located. PAC-1 based on ACGIH TLV-TWA for insoluble or poorly soluble particles not otherwise specified.	DOE (2015)
USAPHC (air-MEG)	1-hr critical: 150 mg/m^3; 1-hr marginal: 35 mg/m^3; 1-hr negligible: 5 mg/m^3 (for lutetium)	Based on 1-hr TEELs. Documentation of the basis for TEEL values was not located.	U.S. APHC (2013)
USAPHC (air-MEG)	1-hr critical: 250 mg/m^3; 1-hr marginal: 50 mg/m^3; 1-hr negligible: 30 mg/m^3 (for lutetium oxide)	Based on 1-hr TEELs. Documentation of the basis for TEEL values was not located.	U.S. APHC (2013)
USAPHC (water-MEG)	1-yr negligible: 7 mg/L (for lutetium)	Derived using 5 L intake rate and subchronic p-RfD from a previous/older PPRTV.	U.S. APHC (2013)
USAPHC (soil-MEG)	1-yr negligible: 1.06×10^5 mg/kg (for lutetium)	Basis: noncancer, not further documented.	U.S. APHC (2013)
Cancer			
IRIS	NV	NA	U.S. EPA (2018a)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2018)

Table 2. Summary of Available Toxicity Values for Lutetium (CASRN 7439-94-3) and Lutetium Compounds

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
CalEPA	NV	NA	CalEPA (2011); CalEPA (2018a); CalEPA (2018b)
ACGIH	NV	NA	ACGIH (2018)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command.
[b]Parameters: MEG = military exposure guideline; PAC = protective action criteria; p-RfD = provisional reference dose; TEEL = temporary emergency exposure limit; TLV = threshold limit value; TWA = time-weighted average.

NA = not applicable; NV = not available; PPRTV = provisional peer-reviewed toxicity value.

Non-date-limited literature searches were conducted in December 2015 and updated in July 2018 for studies relevant to the derivation of provisional toxicity values for soluble lutetium and primarily focused on commonly occurring forms of the compound as follows: lutetium (CASRN 7439-94-3), lutetium chloride (CASRN 10099-66-8), lutetium chloride hexahydrate (CASRN 15230-79-2), lutetium nitrate (CASRN 10099-67-9), lutetium bromide (CASRN 14456-53-2), and lutetium sulfide (CASRN 12163-20-1). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Japan Existing Chemical Data Base (JECDB), European Chemicals Agency (ECHA), Organisation for Economic Co-operation and Development (OECD), Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD High Production Volume (HPV), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA HPV, U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and Defense Technical Information Center (DTIC). Toxicological data were only located for lutetium chloride (CASRN 10099-66-8) and lutetium nitrate (CASRN 10099-67-9).

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for lutetium and its soluble salts and include all potentially relevant repeated-dose short-term-, subchronic-, and chronic-duration studies as well as reproductive and developmental toxicity studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lutetium (CASRN 7439-94-3)

Category[a]	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m^3)							
ND							
Animal							
1. Oral (mg/kg-d)[b]							
Subchronic	**6 M/6 F, CRW rat; lutetium chloride in the diet; 0, 0.01, 0.1, or 1.0%; 90 d**	**M: 0, 5.56, 55.6, or 555.8 (as lutetium);** **F: 0, 6.11, 61.1, or 611.2 (as lutetium)**	**No effect on body weight, hematology, or gross or microscopic pathology of the heart, lung, liver, kidney, pancreas, spleen, adrenals, and small intestine.**	**M: 555.8 (as lutetium)** **F: 611.2 (as lutetium)**	**NDr**	**Haley et al. (1964)**	**PR, PS**
2. Inhalation (mg/m^3)							
ND							

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[b]Dosimetry: Values are presented as ADD of lutetium (in mg Lu/kg-day) for oral noncancer effects.
[c]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

Table 3B. Summary of Potentially Relevant Cancer Data for Soluble Lutetium (CASRN 7439-94-3)					
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**Reference (comments)**	**Notes**
Human					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					
Animal					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m^3)					
ND					

ND = no data.

HUMAN STUDIES

Oral Exposures

No data regarding the toxicity of lutetium to humans following oral exposure have been located. Lutetium texaphyrin (Lu-Tex) has been used in the treatment of age-related macular degeneration. The reported effective dose range was 2−4 mg/kg-day of Lu-Tex (Pharmacyclics, 1999). The texaphyrin moiety is a large porphyrin structure with several side chains and is probably at least as important as the lutetium itself for the compound's biological action. Therefore, any dose-response information for Lu-Tex cannot be applied to the assessment of lutetium alone. Details of the responses encountered in clinical trials were not reported. In addition, even an approximate molecular weight for Lu-Tex cannot be estimated, so the dose range for the lutetium cannot be determined.

Inhalation Exposures

No studies of the toxicity of lutetium to humans exposed by inhalation have been located. The pulmonary toxicity of inhaled rare earth compounds, in general, is the subject of debate, especially with regard to the relative contributions of radioactive contaminants versus stable elements in the development of progressive pulmonary interstitial fibrosis (Beliles, 1994; Haley, 1991). In particular, although it is known that stable rare earth compounds can produce a static, foreign-body-type lesion consistent with benign pneumoconiosis, it is uncertain whether these compounds can also induce interstitial fibrosis that progresses after termination of exposure. Human inhalation toxicity data on stable rare earth elements mainly consist of case reports on workers exposed to multiple lanthanides (Deng et al., 1991; Waring and Watling, 1990; Sulotto et al., 1986; Vogt et al., 1986; Colombo et al., 1983; Vocaturo et al., 1983; Sabbioni et al., 1982; Husain et al., 1980; Kappenberger and Buhlmann, 1975).

ANIMAL STUDIES

Oral Exposures

Haley et al. (1964)

Groups of six male and six female CRW rats were fed 0, 0.01, 0.1, or 1.0% lutetium chloride (purity not reported) in the diet for 90 days (Haley et al., 1964). Although food intake was not reported, growth rates were the same in treated and untreated rats. Compound intake, as lutetium chloride (trichloride, $LuCl_3$), is estimated to have been 8.94, 89.4, or 893.6 mg $LuCl_3$/kg-day in males, and 9.83, 98.3, or 982.7 mg $LuCl_3$/kg-day in females based on reference body weights and food intake.[2] The corresponding lutetium intakes are calculated to be 5.56, 55.6, and 555.8 mg Lu/kg-day for males and 6.11, 61.1, or 611.2 mg Lu/kg-day for females.[3] Body weight and hematology (total erythrocytes, total leukocytes, differential cell count, platelets, hemoglobin [Hb], and hematocrit [Hct]) were measured biweekly, and gross and histological examinations (heart, lung, liver, kidney, pancreas, spleen, adrenal, and small intestine) were performed at the end of the study. No deaths or exposure-related changes were observed in any endpoint examined in either sex. No adverse effects were identified in this study; thus, a lowest-observed-adverse-effect level (LOAEL) could not be identified, and the high doses of 555.8 mg Lu/kg-day (males) and 611.2 mg Lu/kg-day (females) are identified as no-observed-adverse-effect levels (NOAELs). The

[2]Dose estimates for $LuCl_3$ were calculated using the mean reference body weight and food consumption rate values for all rat strains in a subchronic-duration study (U.S. EPA, 1988). Mean reference body weight: 0.235 kg (male) and 0.173 kg (female). Mean reference food consumption: 0.021 kg/day (male) and 0.017 kg/day (female).
[3]Corresponding lutetium doses are calculated using the ratio of molecular weights (Lu:$LuCl_3$ = 174.967:281.326).

lack of effects in this study is consistent with evidence for poor absorption of lutetium and other heavy lanthanide elements (see "Metabolism/Toxicokinetic Studies" section).

Inhalation Exposures

Animal inhalation toxicity data on stable rare earths consist mainly of a few inhalation or intratracheal instillation studies on some rare earth mixtures and some single compounds (Abel and Talbot, 1967; Mogilevskaya and Raikhlin, 1967; Ball and Van Gelder, 1966; Schepers, 1955a, b; Schepers et al., 1955). No lutetium-specific data have been found. A comprehensive assessment of the human and animal data by Haley (1991) concluded that the evidence suggests that inhalation exposure to high concentrations of stable rare earths can produce lesions compatible with pneumoconiosis and progressive pulmonary fibrosis, and that the potential for inducing these lesions is related to chemical type, physicochemical form, and dose and duration of exposure.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Supporting studies on lutetium include acute-duration oral and intraperitoneal (i.p.) lethality studies, an acute-duration study of intravenously (i.v.) injected lutetium, toxicokinetic data, and mechanistic studies. No genotoxicity data for stable lutetium have been located. These studies indicated the following:

- Acute toxicity studies in mice (Haley et al., 1964) suggest slightly greater sensitivity of guinea pigs to lutetium chloride-induced lethality, compared with mice (Graca et al., 1962). An acute toxicity study demonstrated that i.v.-administered lutetium chloride can impair blood clotting (Graca et al., 1964).
- Lutetium is expected to be poorly absorbed through the gastrointestinal (GI) tract [as reviewed by Leggett et al. (2014)]. Once absorbed, lutetium is primarily deposited in bone, where it may persist, and in the liver (Leggett et al., 2014; Nakamura et al., 1997; Müller et al., 1978; Durbin et al., 1956). Data on the excretion of lutetium are not available, but other lanthanides are eliminated primarily via feces following oral exposure, likely due to poor absorption (Nakamura et al., 1991).
- Mechanistic data on lutetium are limited but show that lutetium can occupy calcium binding sites on calmodulin (Buccigross and Nelson, 1986), potentiate gamma-aminobutyric acid (GABA)-induced chloride channels in rat neurons (Ma and Narahashi, 1993), and stimulate fibroblast proliferation (Jenkins et al., 2011).

More detailed descriptions of these data are presented in the "Supporting Toxicity Studies" section below and in Table 4.

Two acute studies (Graca et al., 1964, 1962) assessed the toxicological effects of citrate and edetate complexes of lutetium. The data on these complexes are not discussed in this PPRTV assessment because the citrate and edetate chelating agents may, if dissociated from lutetium, perturb endogenous cation (e.g., calcium, copper, iron, or zinc) homeostasis, resulting in toxic effects that are not attributable to lutetium.

Supporting Toxicity Studies

Acute lethality data for lutetium chloride and lutetium nitrate are shown in Table 4. An oral median lethal dose (LD_{50}) value of 4,441 mg Lu/kg and an i.p. LD_{50} of 197 mg Lu/kg were reported for lutetium chloride in male mice observed for 7 days (Haley et al., 1964). Haley et al. (1964) reported symptoms and mortality information for both orally and i.p.-exposed animals, without

distinguishing by exposure route or dose level. Symptoms included ataxia, writhing, labored respiration, walking on toes with back arched, and sedation. The peak death rate was reached at 48 hours after exposure, but some deaths occurred at 24 hours.

Acute i.p. LD_{50} values for lutetium nitrate were lower in female mice and rats (108 and 125 mg Lu/kg, respectively) observed for 30 days (Bruce et al., 1963) than the value reported by Haley et al. (1964) for male mice exposed i.p. to lutetium chloride. Bruce et al. (1963) observed the mice and rats for a much longer duration and did observe several deaths after the first 8 days (see Table 4), suggesting that LD_{50} values obtained after only 7 days of observation may have underestimated lethality.

Graca et al. (1964) investigated the effects of intravenously-administered chloride salts, citrate complexes, and edetate complexes of lanthanide elements on heart rate, blood pressure, respiration, and clinical hematology in male and female dogs (breed and number/sex not specified). Aqueous solutions of the chloride (equivalent to 5% of the chloride) and chelate complexes of 15 lanthanide elements were injected into a cannula inserted into the left femoral vein. Ten doses of 10 mg $LuCl_3$/kg (6 mg Lu/kg) per dose were injected under anesthesia at 10-minute intervals. For each lanthanide element, groups of three dogs were treated with the chloride. Three separate groups of control dogs were injected with sodium citrate (n = 6), ammonium versenate (n = 6), or Ringer's solution (n = 12) in the same manner as the treated animals. Blood samples were collected from the right femoral vein before treatment and 0, 10, 30, 60, 100, and 160 minutes after treatment for analysis of erythrocyte, leukocyte and differential cell counts, prothrombin and coagulation time, Hb, sedimentation, and Hct. After 160 minutes, the animals were necropsied and tissues were collected for histopathology (liver, spleen, kidney, lung, sternum, mesentery lymph nodes, heart, adrenal, and ovaries or testes). Heart rate, respiration, and blood pressure readings were made at the same intervals as blood samples.

Results for the 15 elements were discussed generally and presented graphically as change over time after treatment (Graca et al., 1964). Some animals died from treatment (14/45 treated with chlorides), but the mortality was not reported by element. Lutetium chloride treatment resulted in a transient spike in blood pressure (150% of pretreatment values) and heart rate (about 130% of pretreatment values) at 60 minutes post-treatment. Respiratory rates appeared to be within control values for lutetium chloride. Lutetium chloride resulted in increases in prothrombin time (to >100 seconds by 100 minutes after treatment, compared to a maximum of 10 seconds for control animals) and coagulation time (to >60 minutes by 1 hour after treatment, compared with a maximum of about 10 minutes for control animals). These effects on prothrombin and coagulation time were generally consistent for almost all the lanthanide elements tested. Visual observation of pooled blood at incision sites provided additional qualitative evidence of the effect of lanthanide elements on clotting parameters, but the study authors did not report the incidence or the specific treatment group(s) where this was observed. Gross and histopathological examinations revealed slight to moderate hyperemia of the lungs, but only in animals treated with chlorides of the lanthanide elements.

Table 4. Acute Lethality Studies

Test	Materials and Methods	Results	Conclusions	References
Acute oral lethality	Lutetium chloride was administered orally to 50 male CF1 mice (doses not reported); the mice were observed for 7 d. No other details were provided.	The peak death rate was reached at 48 hr after exposure, but some deaths occurred at 24 hr. Symptoms of acute lutetium chloride toxicity included ataxia, writhing, labored respiration, walking on toes with back arched, and sedation; the study authors did not specify the doses or exposure routes leading to these effects.	Male mouse oral LD_{50} = 4,441 mg Lu/kg	Haley et al. (1964)
Acute i.p. lethality	Lutetium chloride was administered i.p. to 60 male CF1 mice (doses not reported); the mice were observed for 7 d. No other details were provided.	The peak death rate was reached at 48 hr after exposure, but some deaths occurred at 24 hr. Symptoms of acute lutetium chloride toxicity included ataxia, writhing, labored respiration, walking on toes with back arched, and sedation; the study authors did not specify the doses or exposure routes leading to these effects.	Male mouse i.p. LD_{50} = 197 mg Lu/kg	Haley et al. (1964)
Acute i.p. lethality	Lutetium nitrate was administered i.p. to 30 female CF1 mice (reported as single dose of 0.1% aqueous solution); the animals were observed for 30 d.	For all the lanthanides tested, most mice died within the first 24 hr; however, 26% of the deaths occurred between D 8 and 30 of observation. Symptoms of toxicity were not reported. Gross necropsy of randomly selected survivors of all lanthanide exposure groups showed generalized peritonitis with adhesions and accumulation of ascitic fluid. Necropsy findings specific to lutetium were not reported.	Female mouse i.p. LD_{50} = 108 mg Lu/kg	Bruce et al. (1963)
Acute i.p. lethality	Lutetium nitrate was administered i.p. to 30 female S-D rats (reported as single dose of 0.5% aqueous solution); the animals were observed for 30 d.	For all the lanthanides tested, very few rat deaths occurred within the first 8 d; most deaths occurred between D 10 and 25 of observation. Symptoms of toxicity were not reported. Gross necropsy findings in rats exposed to all the lanthanides included grossly distended abdomens, edema of the limbs, evidence for an inflammatory condition in the peritoneal cavity, with massive adhesions and accumulation of hemorrhagic ascitic fluid. Necropsy findings specific to lutetium were not reported.	Female rat i.p. LD_{50} = 125 mg Lu/kg	Bruce et al. (1963)
Acute i.p. lethality	Lutetium chloride was administered i.p. to CFW albino mice (sex and number not specified) at doses of 188 or 313 mg Lu/kg; the animals were observed for 7 d.	87 and 90% of mice died at 188 and 313 mg Lu/kg, respectively. Mean times to death were 39 and 37 hr, respectively.	Mouse i.p. LD_{50} was not calculated; estimated to be <188 mg Lu/kg	Graca et al. (1962)

Table 4. Acute Lethality Studies

Test	Materials and Methods	Results	Conclusions	References
Acute i.p. lethality	Lutetium chloride was administered i.p. to guinea pigs (strain, sex, and number not specified) at doses of 31, 63, or 94 mg Lu/kg; the animals were observed for 7 d.	5, 28, and 44% of guinea pigs died at 31, 63, and 94 mg Lu/kg, respectively. Mean times to death were 95, 35, and 40 hr, respectively.	Guinea pig i.p. LD_{50} = 101 mg Lu/kg	Graca et al. (1962)
Acute i.v. lethality	10 male and 10 female cats received i.v. doses of lutetium chloride (between 0.6−25 mg Lu/kg). Cardiovascular responses were examined 2 hr later.	No effects occurred at doses up to 6 mg Lu/kg; 5 animals died at 13 mg Lu/kg and at 25 mg Lu/kg, all from complete cardiovascular collapse with respiratory paralysis.	i.v. exposure to lutetium chloride is lethal to cats at a dose of 13 mg Lu/kg	Haley et al. (1964)

i.p. = intraperitoneal; i.v. = intravenous; LD_{50} = median lethal dose; Lu = lutetium; S-D = Sprague-Dawley.

No evidence of hepatotoxicity was noted in rats exposed to a single i.v. dose of lutetium chloride (Nakamura et al., 1997). Doses of 0 or 10 mg Lu/kg (as lutetium chloride) were administered i.v. to 3−5 Wistar-KY rats, and the animals were sacrificed 1 or 3 days later for evaluation of serum chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total cholesterol, phospholipids, triglycerides, total bile acids, and bilirubin) and hepatic lipids (phospholipids, triglycerides, and total cholesterol). Neither serum enzymes nor hepatic lipids were changed from control values in rats treated with lutetium chloride.

Three studies showed that lutetium chloride injections may cause calcification of the injection site, but will not sensitize animals to calcification induced by a histamine liberator. In a very brief report, Haley and Upham (1963) described their finding that nodules of crystalline deposits, possibly containing calcium, occurred at the injection site in guinea pigs given intradermal injections of lutetium chloride. Doses were not specified other than to indicate that a range of 0.5−5 µg was used for each of the lanthanide elements tested. Histopathological examination revealed histiocytes, foreign body giant cells, fibroblasts, and granulation in or surrounding the nodules (Haley and Upham, 1963). Garrett and McClure (1981) reported injection site calcification in groups of 20 male white mice given subcutaneous (s.c.) injections of 0.5 and 10 mg $LuCl_3$ (0.3−6 mg Lu); lower doses did not result in calcification. Microscopic examination of the calcified areas showed mild fibrosis and accumulation of multinucleated giant cells around the calcifications (Garrett and McClure, 1981). Lutetium chloride (3 mg, equivalent to 2 mg Lu) administered intravenously to groups of 10 Sprague-Dawley (S-D) rats (sex not specified) did not sensitize the animals to soft tissue calcification at the site of administration of polymyxin, a histamine liberator (Tuchweber and Savoie, 1968).

Metabolism/Toxicokinetic Studies

The oral absorption of lutetium and other lanthanide elements is very low, probably in part because many of these elements form insoluble hydroxides at neutral pH. While an estimate of the GI absorption of lutetium itself is not available, studies of other lanthanides in a wide variety of species suggested fractional absorption estimates in the range of 10^{-6} to 10^{-3} for all of the lanthanides [reviewed by Leggett et al. (2014)]. Little is known about the absorption of inhaled lanthanides; Leggett et al. (2014) noted that the ionic solutions of lanthanides are not stable at neutral pH, often forming colloidal or hydroxide complexes; such behavior may result in wide variations in lung clearance rates.

The lanthanide elements are typically deposited in the bone, liver, and kidney, although deposition varies with route of exposure. Leggett et al. (2014) reported median molar concentrations of lutetium and other lanthanides in a number of tissues based on data obtained by Zhu et al. (2010) as cited in Leggett et al. (2014) from 68 adult males in China. The nature, magnitude, and routes of lanthanide exposures in this population were not described by Leggett et al. (2014). The highest lutetium concentration was in the rib (3.1 nmol/kg fresh weight), followed by lung (0.97 nmol/kg), thyroid (0.32 nmol/kg), thymus (0.16 nmol/kg), and liver, stomach, fat, skin, and adrenal gland (each at 0.11 nmol/kg); other tissues and blood had lower concentrations. Leggett et al. (2014) indicated that the data were very uncertain due to potential errors in measuring low concentrations and the high variability in the measured concentrations.

Distribution of lutetium after oral exposure has not been studied. After exposure to radioactive lutetium oxides in citrate solution (to increase the speed of absorption from the injection site; 7.3−20 µCi with 0.5−1.9 µg unlabeled carrier) administered by intramuscular

(rats) and i.p. (mice) injection, the highest deposition was in the bone (65 and 35% of injected radioactivity, respectively, 1 day after dosing), with much less (<5%) in the liver (Müller et al., 1978; Durbin et al., 1956). By contrast, 1 day after i.v. exposure of rats to lutetium chloride (10 or 20 mg Lu/kg), lutetium was primarily deposited in the liver (63.5−67% of administered dose) with lesser amounts in bone [11−15%; Nakamura et al. (1997)]. It is not clear whether the differences in distribution resulted from differences in species or strain of animal, route of administration, or form or dose of lutetium administered.

Long-term retention of lutetium has not been studied; however, Müller et al. (1978) estimated the half-lives for elimination of lutetium in female Naval Medical Research Institute (NMRI) mice given single i.p. injections of ^{177}Lu (1−60 mCi/kg as lutetium oxide fused with potassium bisulfate, with 0.5 mg/kg stable lutetium carrier) and sacrificed 1, 7, or 15 days later. The estimated half-life for elimination of lutetium was 5 days for the liver, spleen, and kidneys and 50 days for the femur (Müller et al., 1978). Durbin et al. (1956) reported that the half-life for elimination from the skeleton of the heavier lanthanides (lutetium is the heaviest) was about 2.5 years in rats, based on data collected for ^{160}terbium (Tb) and ^{170}thulium (Tm) over 256 days. The skeletal half-life estimated for lutetium by Müller et al. (1978) is much lower than the skeletal half-life (2.5 years) estimated by Durbin et al. (1956) for heavy lanthanides, possibly because the lutetium estimate was based on a much shorter time frame. Müller et al. (1978) collected data on bone radioactivity over only 15 days, while Durbin et al. (1956) collected data on bone radioactivity for five lanthanides over 256 days. Graphical display of the bone radioactivity in the study by Durbin et al. (1956) indicated that some lanthanides (e.g., promethium [Pm], cerium [Ce]) exhibited an initial decline in skeletal radioactivity content followed by a plateau, so estimating a half-life using only data from the initial period after dosing could lead to underestimation.

Data on the excretion of lutetium in humans or animals have not been located. After oral administration of other lanthanide elements (yttrium [Y], dysprosium [Dy], europium [Eu], and ytterbium [Yb], as their chloride hexahydrates) to male Wistar rats, none of these elements were detected in urine, and 92−98% of administered doses (100 and 1,000 mg lanthanide/kg) was eliminated in the feces within 7 days [Nakamura et al. (1991); published in Japanese with English abstract and tables], likely reflecting poor absorption through the oral route of exposure. Elimination of lutetium is likely to follow a similar pattern.

Mechanistic Studies

Buccigross and Nelson (1986) assessed the binding of lanthanide elements to calmodulin in an electron paramagnetic resonance (EPR) study and observed that lutetium binds to calmodulin in a similar manner as calcium does, with preference for the two high-affinity binding sites on calmodulin. Calmodulin is a protein that plays an integral role in regulating a wide variety of physiological processes, including inflammation, metabolism, apoptosis, smooth muscle contraction, memory, and immune response via calcium-dependent signal transduction. Thus, interference with calmodulin function, and/or competition and displacement of calcium from binding to this protein could have pluripotent adverse impacts. Evidence for lutetium effects on calcium transport was seen in the study by Nakamura et al. (1997), who reported significantly increased concentrations of calcium in the liver, spleen, lungs, and kidneys in rats given lutetium chloride intravenously. In contrast, concentrations of phosphorus, zinc, copper, sodium, and potassium were not affected by lutetium administration (Nakamura et al., 1997).

Ma and Narahashi (1993) tested a series of lanthanide elements, including lutetium, for the ability to potentiate GABA-induced chloride currents in rat dorsal ganglion neurons in vitro. Of the seven lanthanides tested (lanthanum [La], Ce, neodymium [Nd], Eu, Tb, erbium [Er], and Lu), lutetium induced the strongest increase in GABA-induced current (12.6-fold compared with control). Lutetium and the other lanthanides were also able to induce an inward chloride current in the absence of GABA. In both assays, the strength of response declined monotonically with molecular weight (from Lu to La). Effects on GABA-induced currents suggest the possibility of neurological effects from lutetium exposure.

Jenkins et al. (2011) tested chloride salts of 14 lanthanide elements, including lutetium, for the ability to stimulate proliferation of dermal fibroblasts. Concentrations of 10 and 50 µM lutetium resulted in significantly increased proliferation of fibroblasts, but not of epidermal keratinocytes (Jenkins et al., 2011). Stimulation of fibroblast proliferation may play a role in localized fibrotic responses seen in guinea pigs and mice exposed to lutetium chloride by intradermal and s.c. injection, respectively (Garrett and McClure, 1981; Haley and Upham, 1963).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively, for soluble lutetium. Data were available to derive a subchronic provisional reference dose (p-RfD) for soluble lutetium, but no other reference values.

Table 5. Summary of Noncancer Reference Values for Soluble Lutetium (CASRN 7439-94-3)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Subchronic p-RfD for soluble lutetium (mg Lu/kg-d)	Rat/M	None observed	4×10^{-1}	NOAEL	133.4	300	Haley et al. (1964)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

HED = human equivalent dose; Lu = lutetium; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; POD = point of departure; UF_C = composite uncertainty factor.

Table 6. Summary of Cancer Reference Values for Soluble Lutetium (CASRN 7439-94-3)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF $(mg/kg\text{-}d)^{-1}$	NDr			
p-IUR $(mg/m^3)^{-1}$	NDr			

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

Derivation of a Subchronic Provisional Reference Dose

Information on the toxicity of repeated oral exposure to lutetium is limited to a single subchronic-duration (90-day) dietary study of lutetium chloride in rats (Haley et al., 1964). No deaths or exposure-related changes were observed in any endpoint examined in either sex (see study summary above); therefore, 555.8 mg Lu/kg-day and 611.2 Lu/kg-day are identified as NOAELs in male and female rats, respectively. No LOAELs could be identified. The only other information available on the oral toxicity of lutetium is an oral LD_{50} in male mice (4,416 mg Lu/kg).

Since no LOAEL could be identified from the Haley et al. (1964) principal study or the soluble lutetium database, it is unknown where a true LOAEL may exist on the dose-response curve for male and female rats in Haley et al. (1964), and it is unknown how a true LOAEL for each sex would compare to each other, it is prudent in this case to select the more sensitive and health protective male rat NOAEL value of 555.8 mg Lu/kg-day reported by Haley et al. (1964)

as the point of departure (POD) to derive the subchronic p-RfD for soluble lutetium. The NOAEL is converted to a human equivalent dose (HED) according to current U.S. EPA (2011b) guidance. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the U.S. EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an oral reference dose (RfD) from effects that are not portal-of-entry effects. As the critical effect for lutetium is not known, it is assumed that body-weight scaling is appropriate.

Following U.S. EPA (2011b) guidance, the POD is converted to a HED through the application of a dosimetric adjustment factor (DAF)[4] derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.235 kg for rats and a reference BW_h of 70 kg for humans, the resulting DAF is 0.24 (U.S. EPA, 2011b). Applying this DAF to the NOAEL of 555.8 mg Lu/kg-day yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg Lu/kg-day)} \times \text{DAF} \\ &= 555.8 \text{ mg Lu/kg-day} \times 0.24 \\ &= 133.4 \text{ mg Lu/kg-day} \end{aligned}$$

The subchronic p-RfD for soluble lutetium was derived using the POD (HED) and a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 10):

$$\begin{aligned} \textbf{Subchronic p-RfD for Soluble Lutetium} &= \text{POD (HED)} \div UF_C \\ &= 133.4 \text{ mg Lu/kg-day} \div 300 \\ &= \mathbf{4 \times 10^{-1} \text{ mg Lu/kg-day}} \end{aligned}$$

Table 7 summarizes the uncertainty factors for the subchronic p-RfD for soluble lutetium.

[4]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Table 7. Uncertainty Factors for the Subchronic p-RfD for Soluble Lutetium

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following oral lutetium exposure. The toxicokinetic uncertainty has been accounted for by calculating a HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to account for the limited toxicity database for soluble lutetium, which consists of only a single subchronic-duration rat dietary study using $LuCl_3$.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of lutetium in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level;
NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose;
UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor;
UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

The confidence in the subchronic p-RfD for soluble lutetium is low, as described in Table 8.

Table 8. Confidence Descriptors for the Subchronic p-RfD for Soluble Lutetium

Confidence Categories	Designation	Discussion
Confidence in principal study	L	Confidence in the principal study is low. While it is a peer-reviewed study using three dose groups plus a control group, group sizes were small (6/sex/group). The test material was administered in the diet, but food consumption was not measured, so the doses are estimated. Furthermore, the study did not evaluate clinical chemistry or organ weights, histopathology examinations were limited to major organs (heart, lung, liver, kidney, spleen, pancreas, adrenal glands, and small intestine), and a LOAEL was not identified.
Confidence in database	L	Confidence in the database for lutetium is low. The relevant database consists of a single subchronic-duration rat study; the only other information on oral toxicity is an oral LD_{50} in mice. The available study (Haley et al., 1964) did not examine the stomach for histopathology, and the stomach has been identified as a target organ for other lanthanide elements, including gadolinium and europium (Ogawa et al., 1995; Ogawa et al., 1992). In addition, the neurotoxicity and neurodevelopmental effects of lutetium have not been examined. Lutetium was shown to both potentiate GABA-induced chloride currents and induce inward currents in rat neurons (Ma and Narahashi, 1993), suggesting potential for neurotoxic effects.
Confidence in subchronic p-RfD[a]	L	The overall confidence in the subchronic p-RfD is low.

[a]The overall confidence cannot be greater than the lowest entry in the table (low).

GABA = gamma-aminobutyric acid; L = low; LD_{50} = median lethal dose;
LOAEL = lowest-observed-adverse-effect level; p-RfD = provisional reference dose.

Toxicological data on other salts of lutetium are limited to i.p. LD_{50} studies of lutetium nitrate in mice and rats (Bruce et al., 1963). Because the fundamental determinant of the toxicity of soluble lutetium compounds is expected to be due to lutetium metal itself, the toxicity of such soluble compounds is directly related to the relative molecular weight contribution from lutetium. Therefore, the subchronic p-RfD derived above for soluble lutetium is applicable to soluble lutetium compounds (e.g., salts) following application of a molecular-weight adjustment and appropriate stoichiometric calculations.

Derivation of a Chronic Provisional Reference Dose

A chronic p-RfD was not derived for soluble lutetium for several reasons. First, there are notable deficiencies in the database including (1) it is limited to a single subchronic-duration (90-day) dietary study of lutetium chloride in rats (Haley et al., 1964), with no studies of chronic-duration exposure to soluble lutetium in any species, and (2) no LOAEL was able to be identified from this only available study. Additionally, although long-term retention of lutetium following oral exposure has not been examined, studies using injected radioactive lutetium oxide (chelated in a citrate solution to increase the speed of absorption from the site of injection) reported substantial deposition of ^{177}Lu to bone (Müller et al., 1978; Durbin et al., 1956). Durbin et al. (1956) estimated a half-life of 2.5 years for elimination of heavier lanthanides (lutetium is

the heaviest lanthanide) from the skeleton. Thus, the potential for prolonged retention of lutetium in the body bolsters the uncertainty surrounding the extrapolation of no observed toxicological effects after subchronic-duration soluble lutetium exposure to potential effects following chronic-duration exposure. Taken together, these uncertainties collectively preclude the derivation of a chronic p-RfD for soluble lutetium.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No pertinent data regarding the toxicity of repeated inhalation exposure to soluble lutetium are found in the available literature. Derivation of a provisional reference concentration (p-RfC) for soluble lutetium is precluded by the lack of appropriate inhalation toxicity data.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No carcinogenicity or genotoxicity data have been located for soluble lutetium. The cancer weight-of-evidence (WOE) descriptor for soluble lutetium is presented in Table 9.

Table 9. Cancer WOE Descriptor for Soluble Lutetium (CASRN 7439-94-3)

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no animal studies to support this.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	There are no animal studies to support this.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No studies are available that evaluated carcinogenic effects in humans or animals exposed to lutetium.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available.

NA = not applicable; NS = not selected; WOE = weight of evidence.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of quantitative estimates of cancer risk for soluble lutetium is precluded by the lack of data demonstrating carcinogenicity associated with lutetium exposure.

APPENDIX A. REFERENCES

Abel, M; Talbot, RB. (1967). Gadolinium oxide inhalation by guinea pigs: A correlative functional and histopathologic study. J Pharmacol Exp Ther 157: 207-213.

ACGIH (American Conference of Governmental Industrial Hygienists). (2018). 2018 TLVs and BEIs. Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH. http://www.acgih.org/forms/store/ProductFormPublic/2018-tlvs-and-beis

ATSDR (Agency for Toxic Substances and Disease Registry). (2018). Minimal risk levels (MRLs). June 2018. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from http://www.atsdr.cdc.gov/mrls/index.asp

Ball, RA; Van Gelder, G. (1966). Chronic toxicity of gadolinium oxide for mice following exposure by inhalation. Arch Environ Health 13: 601-608. http://dx.doi.org/10.1080/00039896.1966.10664625

Banerjee, S; Pillai, MR; Knapp, FF. (2015). Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications [Review]. Chem Rev 115: 2934-2974. http://dx.doi.org/10.1021/cr500171e

Beliles, RP. (1994). The lanthanides. In GD Clayton; FE Clayton (Eds.), Patty's industrial hygiene and toxicology: Volume 2: Part C, toxicology (4th ed., pp. 2048-2065). New York, NY: John Wiley & Sons, Inc.

Bruce, DW; Hietbrink, BE; DuBois, KP. (1963). The acute mammalian toxicity of rare earth nitrates and oxides. Toxicol Appl Pharmacol 5: 750-759. http://dx.doi.org/10.1016/0041-008X(63)90067-X

Buccigross, JM; Nelson, DJ. (1986). EPR studies show that all lanthanides do not have the same order of binding to calmodulin. Biochem Biophys Res Commun 138: 1243-1249. http://dx.doi.org/10.1016/S0006-291X(86)80416-8

Bunzli, JCG. (2013). Lanthanides. In RE Kirk; DF Othmer (Eds.), Kirk-Othmer Encyclopedia of Chemical Technology (4th ed.). New York, NY: John Wiley & Sons, Inc. http://dx.doi.org/10.1002/0471238961.1201142019010215.a01.pub3

CalEPA (California Environmental Protection Agency). (2011). Hot spots unit risk and cancer potency values. Appendix A. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://standards.nsf.org/apps/group_public/download.php?document_id=19121

CalEPA (California Environmental Protection Agency). (2016). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 28 2016. Sacramento, CA: Office of Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/air/allrels.html

CalEPA (California Environmental Protection Agency). (2018a). Chemicals known to the state to cause cancer or reproductive toxicity May 25, 2018. (Proposition 65 list). Sacramento, CA: Office of Enironmental Health Hazard Assessment. http://oehha.ca.gov/proposition-65/proposition-65-list

CalEPA (California Environmental Protection Agency). (2018b). OEHHA toxicity criteria database. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/tcdb/index.asp

Colombo, F; Zanoni, M; Vocaturo, G; Rodi, F; Satta, A; Pietra, R; Sabbioni, E. (1983). Pneumoconiosi da terre rare. Med Lav 74: 191-197.

Deng, JF; Sinks, T; Elliot, L; Smith, D; Singal, M; Fine, L. (1991). Characterisation of respiratory health and exposures at a sintered permanent magnet manufacturer. Br J Ind Med 48: 609-615.

DOE (U.S. Department of Energy). (2015). Table 3: Protective Action Criteria (PAC) Rev. 28 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. December 2015. Retrieved from http://www.atlintl.com/DOE/teels/teel/Revision_28_Table3.pdf

Durbin, PW; Williams, MH; Gee, M; Newman, RH; Hamilton, JG. (1956). Metabolism of the lanthanons in the rat. Proc Soc Exp Biol Med 91: 78-85.

ECHA (European Chemicals Agency). (2018). Registered substances: Helsinki, Finland. Retrieved from http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Evans, CH. (1990). Chemical properties of biochemical relevance. In Biochemistry of the lanthanides. New York: Springer. http://dx.doi.org/10.1007/978-1-4684-8748-0

Garrett, IR; McClure, J. (1981). Lanthanide-induced calcergy. J Pathol 135: 267-275. http://dx.doi.org/10.1002/path.1711350404

Graca, JG; Davison, FC; Feavel, JB. (1962). Comparative toxicity of stable rare earth compounds. II. Effect of citrate and edetate complexing on acute toxicity in mice and guinea pigs. Arch Environ Health 5: 437-444.

Graca, JG; Davison, FC; Feavel, JB. (1964). Comparative toxicity of stable rare earth compounds. III. Acute toxicity of intravenous injections of chlorides and chelates in dogs. Arch Environ Health 8: 555-564.

Haley, PJ. (1991). Pulmonary toxicity of stable and radioactive lanthanides. Health Phys 61: 809-820.

Haley, TJ; Komesu, N; Efros, M; Koste, L; Upham, HC. (1964). Pharmacology and toxicology of lutetium chloride. J Pharm Sci 53: 1186-1188.

Haley, TJ; Upham, HC. (1963). Skin reaction to intradermal injection of rare earths [Letter]. Nature 200: 271. http://dx.doi.org/10.1038/200271a0

Haynes, WM. (2014). Lutetium. In CRC Handbook of Chemistry and Physics (95th ed.). Boca Raton, FL: CRC Press.

Husain, MH; Dick, JA; Kaplan, YS. (1980). Rare earth pneumoconiosis. J Soc Occup Med 30: 15-19. http://dx.doi.org/10.1093/occmed/30.1.15

IARC (International Agency for Research on Cancer). (2018). IARC Monographs on the evaluation of carcinogenic risk to humans. Retrieved from http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

IPCS (International Programme on Chemical Safety). (2018). INCHEM: Chemical safety information from intergovernmental organizations [Database]. Geneva, Switzerland: World Health Organization, Canadian Centre for Occupational Health and Safety. Inter-Organization Programme for the Sound Management of Chemicals. Retrieved from http://www.inchem.org/

Jenkins, W; Perone, P; Walker, K; Bhagavathula, N; Aslam, MN; Dasilva, M; Dame, MK; Varani, J. (2011). Fibroblast response to lanthanoid metal ion stimulation: Potential contribution to fibrotic tissue injury. Biol Trace Elem Res 144: 621-635. http://dx.doi.org/10.1007/s12011-011-9041-x

Kappenberger, L; Buhlmann, AA. (1975). Lungenveranderungen durch <<Seltene Erden>> [Pulmonary lesions due to "rare earths"]. Swiss Med Wkly 105: 1799-1801.

Leggett, R; Ansoborlo, E; Bailey, M; Gregoratto, D; Paquet, F; Taylor, D. (2014). Biokinetic data and models for occupational intake of lanthanoids [Review]. Int J Radiat Biol 90: 996-1010. http://dx.doi.org/10.3109/09553002.2014.887868

Lewis, RJ, Sr; Hawley, GG. (2007). Lutetium. In RJ Lewis, Sr.; GG Hawley (Eds.), Hawley's condensed chemical dictionary (15th ed., pp. 771). Hoboken, NJ: John Wiley & Sons. http://dx.doi.org/10.1002/9780470114735.hawley10037

Ma, JY; Narahashi, T. (1993). Enhancement of gamma-aminobutyric acid-activated chloride channel currents by lanthanides in rat dorsal root ganglion neurons. J Neurosci 13: 4872-4879.

Metall Rare Earth (Metall Rare Earth Limited). (2015). Metall Rare Earth Limited. Lutetium. Shenzhen, China. Retrieved from http://www.metall.com.cn/re/Lu.htm

Mogilevskaya, OY; Raikhlin, NT. (1967). Rare earth metals. In ZI Izrael'son (Ed.), Toxicology of the rare metals. Jerusalem, Israel: Israel Program for Scientific Translations.

Müller, WA; Linzner, U; Schäffer, EH. (1978). Organ distribution studies of lutetium-177 in mouse. Int J Nucl Med Biol 5: 29-31.

Nakamura, Y; Tsumura-Hasegawa, Y; Tonogai, Y; Kanamoto, M; Tsuboi, N; Murakami, K; Ito, Y. (1991). [Excretion of dysprosium, europoium, ytterbium and yttrium in the rat after oral administration]. Eisei Kagaku 37: 418-425. http://dx.doi.org/10.1248/jhs1956.37.418

Nakamura, Y; Tsumura, Y; Tonogai, Y; Shibata, T; Ito, Y. (1997). Differences in behavior among the chlorides of seven rare earth elements administered intravenously to rats. Toxicol Sci 37: 106-116.

NIOSH (National Institute for Occupational Safety and Health). (2016). NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Atlanta, GA: Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). (2016). 14th Report on carcinogens. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

O'Neil, MJ. (2013). Lutetium. In MJ O'Neill; PE Heckelman; PH Dobbelaar; KJ Roman; CM Kenney; LS Karaffa (Eds.), The Merck index (15th ed., pp. 1045). Cambridge, UK: Royal Society of Chemistry. https://www.rsc.org/Merck-Index/searchresults?searchterm=Lutetium%20

Ogawa, Y; Suzuki, S; Naito, K; Saito, M; Kamata, E; Hirose, A; Ono, A; Kaneko, T; Chiba, M; Inaba, Y. (1995). Toxicity study of europium chloride in rats. J Environ Pathol Toxicol Oncol 14: 1-9.

Ogawa, Y; Suzuki, S; Naito, K; Saito, N; Hirose, A; Kaneko, T; Kurokama, Y. (1992). A 28-day repeated dose toxicity test of europium and gadolinium in Wistar rats in comparison with lanthanum and yttrium. J Toxicol Sci 17: 331.

OSHA (Occupational Safety & Health Administration). (2017a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor. https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286

OSHA (Occupational Safety & Health Administration). (2017b). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. (OSHA standard 1910.1000, 29 CFR). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

Pharmacyclics. (1999). Pharmacyclics annouces clinical results with lutetium texaphyrin for treatment of age-related macular degeneration. Sunnyvale, CA: Pharmacyclics. http://files.shareholder.com/downloads/PCYC/0x0x44528/64d815ba-9c2e-43bc-844f-0ae2fc9e702c/PCYC_News_1999_6_28_General.pdf

Sabbioni, E; Pietra, R; Gaglione, P; Vocaturo, G; Columbo, F; Zanoni, M; Rodi, F. (1982). Long-term occupational risk of rare-earth pneumoconiosis: a case report as investigated by neutron activation analysis. Sci Total Environ 26: 19-32.

Schepers, GW. (1955a). The biological action of rare earths. I. The experimental pulmonary histopathology produced by a blend having a relatively high oxide content. AMA Arch Ind Health 12: 301-305.

Schepers, GW. (1955b). The biological action of rare earths. II. The experimental pulmonary histopathology produced by a blend having a relatively high fluoride content. AMA Arch Ind Health 12: 306-316.

Schepers, GW; Delahant, AB; Redlin, AJ. (1955). An experimental study of the effects of rare earths on animal lungs. AMA Arch Ind Health 12: 297-300.

Sulotto, F; Romano, C; Berra, A; Botta, GC; Rubino, GF; Sabbioni, E; Pietra, R. (1986). Rare-earth pneumoconiosis: a new case. Am J Ind Med 9: 567-575.

TaekRim, K; HoKoo, K; SunPark, J. (2013). Toxicological evaluations of rare earths and their health impacts to workers: a literature review. Saf Health Work 4: 12-26. http://dx.doi.org/https://doi.org/10.5491/SHAW.2013.4.1.12

Tuchweber, B; Savoie, L. (1968). Rare earth metals and soft-tissue calcification. Proc Soc Exp Biol Med 128: 473-476.

U.S. APHC (U.S. Army Public Health Command). (2013). Environmental health risk assessment and chemical exposure guidelines for deployed military personnel. (Technical guide 230, 2013 revision). Aberdeen Proving Ground, MD. https://phc.amedd.army.mil/PHC%20Resource%20Library/TG230-DeploymentEHRA-and-MEGs-2013-Revision.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1988). Recommendations for and documentation of biological values for use in risk assessment (pp. 1-395). (EPA/600/6-87/008). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855

U.S. EPA (U.S. Environmental Protection Agency). (2002). A review of the reference dose and reference concentration processes (pp. 1-192). (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. http://www.epa.gov/osa/review-reference-dose-and-reference-concentration-processes

U.S. EPA (U.S. Environmental Protection Agency). (2011a). Health effects assessment summary tables for superfund (HEAST). Available online at https://epa-heast.ornl.gov/heast.php (accessed December 13, 2017).

U.S. EPA (U.S. Environmental Protection Agency). (2011b). Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose (pp. 1-50). (EPA/100/R11/0001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum, Office of the Science Advisor. https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose

U.S. EPA (U.S. Environmental Protection Agency). (2012). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water. https://rais.ornl.gov/documents/2012_drinking_water.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2018a). Integrated risk information system (IRIS) [Database]. Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. Retrieved from http://www.epa.gov/iris/

U.S. EPA (U.S. Environmental Protection Agency). (2018b). The Toxic Substances Control Act's public inventory (TSCA inventory). Retrieved from https://www.epa.gov/tsca-inventory/how-access-tsca-inventory#download

USGS (U.S. Geological Survey). (2016). 2013 Mineral yearbook. Rare earths [advance release]. http://minerals.usgs.gov/minerals/pubs/commodity/rare_earths/myb1-2013-raree.pdf

Vocaturo, G; Colombo, F; Zanoni, M; Rodi, F; Sabbioni, E; Pietra, R. (1983). Human exposure to heavy metals: rare earth pneumoconiosis in occupational workers. Chest 83: 780-783. http://dx.doi.org/10.1378/chest.83.5.780

Vogt, P; Spycher, MA; Ruttner, JR. (1986). Pneumokoniose durch <<Seltene Erden>> (cer-pneumokoniose) [Pneumoconiosis caused by "rare earths" (cer-pneumoconiosis)]. Swiss Med Wkly 116: 1303-1308.

Waring, PM; Watling, RJ. (1990). Rare earth deposits in a deceased movie projectionist: a new case of rare earth pneumoconiosis? [Review]. Med J Aust 153: 726-730.

WHO (World Health Organization). (2018). Online catalog for the Environmental Health Criteria (EHC) monographs. Geneva, Switzerland: World Health Organization (WHO). Retrieved from http://www.who.int/ipcs/publications/ehc/en/