EPA/690/R-18/004 | September 27, 2018 | FINAL

United States
Environmental Protection
Agency

Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Soluble Lanthanum (CASRN 7439-91-0)

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

United States Environmental Protection Agency

EPA/690/R-18/004
FINAL
09-27-2018

Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Soluble Lanthanum
(CASRN 7439-91-0)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Q. Jay Zhao, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Jeffry L. Dean, PhD
National Center for Environmental Assessment, Cincinnati, OH

Jeff Swartout
National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

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

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS iv
BACKGROUND 1
DISCLAIMERS 1
QUESTIONS REGARDING PPRTVs 1
INTRODUCTION 2
REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER) 8
HUMAN STUDIES 17
ANIMAL STUDIES 17
Oral Exposures 17
Inhalation Exposures 33
OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS) 33
Genotoxicity 45
Acute and Short-Term-Duration Oral Studies 45
Other Route Toxicity Studies 45
Mode-of-Action/Mechanistic Studies 46
Metabolism/Toxicokinetic Studies 47
DERIVATION OF PROVISIONAL VALUES 50
DERIVATION OF ORAL REFERENCE DOSES 50
Derivation of a Subchronic Provisional Reference Dose 50
Derivation of a Chronic Provisional Reference Dose 54
DERIVATION OF INHALATION REFERENCE CONCENTRATIONS 56
CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR 56
DERIVATION OF PROVISIONAL CANCER POTENCY VALUES 57
APPENDIX A. SCREENING PROVISIONAL VALUES 58
APPENDIX B. DATA TABLES 59
APPENDIX C. BENCHMARK DOSE MODELING RESULTS 71
APPENDIX D. REFERENCES 89

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 LANTHANUM (CASRN 7439-91-0) AND SOLUBLE SALTS

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.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. 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

Lanthanum, CASRN 7439-91-0, a member of the lanthanide series, is a metallic element with an atomic number of 57. Lanthanum salts are used in electronic devices, pyrophoric alloys, rocket propellants, reducing agent catalyst for conversion of nitrogen oxides to nitrogen in exhaust gases (usually in combination with cobalt, lead, or other metals), and phosphors in X-ray screens (Lewis and Hawley, 2007). Lanthanum is listed on U.S. EPA's Toxic Substances Control Act's (TSCA) public inventory (U.S. EPA, 2018b) and is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018).

Lanthanum occurs naturally in the earth's crust at a concentration of approximately 39 ppm (Bunzli, 2013). Lanthanides, such as lanthanum, typically occur in compounds as trivalent cations in carbonates, oxides, phosphates, and silicates (USGS, 2016). Lanthanum is found in several minerals including cerite, monazite, allanite, and bastnasite. Monazite and bastnasite are lanthanum's principal ores in which the element occurs in percentages up to 25 and 38%, respectively (Haynes, 2014). Monazite is digested using caustic soda to obtain the lanthanides as hydroxides. They are then treated with hydrochloric or nitric acid to remove thorium and other elements, and finally further processed to recover the individual lanthanides. A similar process can be used for bastnasite (Bunzli, 2013).

Lanthanum is a silvery-white, malleable, ductile metal that is soft enough to be cut with a knife. It oxidizes rapidly when exposed to air. Lanthanum reacts slowly with cold water and more rapidly with hot water (Haynes, 2014). Reaction with water forms lanthanum hydroxide and hydrogen. Lanthanum metal is soluble in acids (Lewis and Hawley, 2007). Table 1 summarizes its physicochemical properties. Like other lanthanides, lanthanum forms mostly ionic compounds, has a high preference to bind 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 salts of hydroxide, carbonate, phosphate, and fluoride are insoluble (Evans, 1990).

This document describes data for soluble lanthanum. The insoluble lanthanum salts are expected to differ substantially from the soluble salts with respect to absorption, distribution, and elimination, so are not the subject of this PPRTV assessment. Table 1 summarizes the physicochemical properties of lanthanum and four of its commonly occurring soluble salts.

Lanthanum chloride ($LaCl_3$), CASRN 10099-58-8, is a white, transparent, hygroscopic, crystalline solid that is soluble in water. It is produced by the treatment of lanthanum carbonates, or oxides, with hydrochloric acid in an atmosphere of dry hydrogen chloride. Anhydrous lanthanum chloride is often used to prepare the metal (Lewis and Hawley, 2007). Data for lanthanum chloride and its heptahydrate ($LaCl_3 \cdot 7H_2O$), CASRN 10025-84-0, are shown in Table 1.

Lanthanum nitrate hexahydrate [$La(NO_3)_3 \cdot 6H_2O$], CASRN 10277-43-7, is a white, hygroscopic, crystalline solid that is soluble in water, alcohol, and acids. It is used as an antiseptic and in gas mantles (Lewis and Hawley, 2007). Data for lanthanum nitrate hexahydrate

are shown in Table 1; no data on the physicochemical properties of anhydrous lanthanum nitrate could be located.

Lanthanum acetate hydrate [$La(CH_3COO)_3 \cdot H_2O$], CASRN 100587-90-4, is a white powder that is soluble in water and acid (Lewis and Hawley, 2007). It is described as being "somewhat less soluble" than the chlorides and nitrates (Bunzli, 2013). Data for lanthanum acetate hydrate are shown in Table 1; no data on the physicochemical properties of anhydrous lanthanum acetate could be located.

Soluble lanthanum salts, once dissolved in aqueous solution and biological systems, would rapidly form La 3^+ ions with bound water molecules. The solubility of La 3^+ in aqueous solution is pH dependent. At pH below ~7.5, the La 3^+ ion is bound to water molecules as its soluble aqua ion [$La(H_2O)_8^{3+}$], which would be the predominant lanthanum species found in the stomach (pH 1−2). Above pH 7.5, as would be found in the small intestines and blood, lanthanum will begin to precipitate out of solution as the bound water molecules are converted to hydroxide ions [$La(OH)_3(H_2O)_5$]. In biological systems, La 3^+ ions may also bind to other oxygen donor molecules such as carboxylic acids (proteins) and phosphates (nucleic acids) (Evans, 1990).

Table 1. Physicochemical Properties of Lanthanum (CASRN 7439-91-0) and Soluble Salts[a, b]

Property (unit)	Lanthanum	Lanthanum Chloride, Anhydrous	Lanthanum Chloride Heptahydrate	Lanthanum Nitrate Hexahydrate	Lanthanum Acetate Hydrate
CASRN	7439-91-0	10099-58-8	10025-84-0	10277-43-7	100587-90-4
Formula	La	$LaCl_3$	$LaCl_3 \cdot 7H_2O$	$La(NO_3)_3 \cdot 6H_2O$	$La(CH_3COO)_3 \cdot H_2O$
Physical state	Solid	Solid	Solid	Solid	Solid[c]
Boiling point (°C)	3,464	NA	NA	NA	NA
Melting point (°C)	920	858	91 (decomposes)	~40 (decomposes)	NV
Density (g/cm^3 at 25°C)	6.15	3.84	NV	NV	NV
pH at which precipitation starts [0.1 M $La(NO_3)_3$]	NA	NA	NA	NA	NA
Vapor pressure (mm Hg at 25°C)	NA	NV	NV	NV	NV
Solubility in water (mg/L at 25°C)	Insoluble	957,000	957,000	2,000,000	Soluble[c]
Atomic or formula weight (g/mol)	138.91	245.27	371.37	433.01	334.05
Flash point (°C)	NA	NV	NV	NV	NV

[a]Properties for lanthanum chloride hexahydrate, anhydrous lanthanum nitrate, and anhydrous lanthanum acetate were not available.
[b]Haynes (2014), unless otherwise specified.
[c]Lewis and Hawley (2007).

La = lanthanum; $La(CH_3COO)_3$ = lanthanum acetate; $LaCl_3$ = lanthanum chloride; $La(NO_3)_3$ = lanthanum nitrate; NA = not applicable; NV = not available.

A summary of available toxicity values for lanthanum and lanthanum compounds from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Lanthanum (CASRN 7439-91-0) and Lanthanum Compounds

Source (parameter)[a, b]		Value (applicability)	Notes	Reference(s)
Noncancer				
IRIS		NV	NA	U.S. EPA (2018a)
HEAST		NV	NA	U.S. EPA (2011)
DWSHA		NV	NA	U.S. EPA (2012)
ATSDR		NV	NA	ATSDR (2018)
IPCS		NV	NA	IPCS (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)	Lanthanum	PAC-1: 30 mg/m^3; PAC-2: 330 mg/m^3; PAC-3: 2,000 mg/m^3	Based on TEELs	DOE (2016)
	Lanthanum nitrate hexahydrate	PAC-1: 1.3 mg/m^3; PAC-2: 15 mg/m^3; PAC-3: 89 mg/m^3		
	Lanthanum chloride	PAC-1: 7.1 mg/m^3; PAC-2: 78 mg/m^3; PAC-3: 470 mg/m^3		
	Lanthanum nitrate	PAC-1: 14 mg/m^3; PAC-2: 150 mg/m^3; PAC-3: 890 mg/m^3		
USAPHC (air-MEG)	Lanthanum	1-hr critical: 250 mg/m^3; 1-hr marginal: 50 mg/m^3; 1-hr negligible: 30 mg/m^3	Based on TEELs	U.S. APHC (2013)
	Lanthanum nitrate hexahydrate	1-hr critical: 150 mg/m^3; 1-hr marginal: 35 mg/m^3; 1-hr negligible: 5 mg/m^3		
	Lanthanum chloride	1-hr critical: 500 mg/m^3; 1-hr marginal: 150 mg/m^3; 1-hr negligible: 20 mg/m^3		
Cancer				
IRIS		NV	NA	U.S. EPA (2018a)
HEAST		NV	NA	U.S. EPA (2011)
DWSHA		NV	NA	U.S. EPA (2012)

Table 2. Summary of Available Toxicity Values for Lanthanum (CASRN 7439-91-0) and Lanthanum Compounds

Source (parameter)[a, b]	Value (applicability)	Notes	Reference(s)
NTP	NV	NA	NTP (2016)
IARC	NV	NA	IARC (2018)
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 = U.S. 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.

NA = not applicable; NV = not available; TEEL = temporary emergency exposure limit.

Non-date-limited literature searches were conducted in January 2016 and updated in July 2018 for studies relevant to the derivation of provisional toxicity values for soluble lanthanum and primarily focused on commonly occurring forms of the compound as follows: lanthanum (CASRN 7439-91-0), lanthanum ion (La^{2+}; CASRN 17643-88-8), lanthanum ion (La^{3+}; CASRN 16096-89-2), and soluble or moderately soluble lanthanum salts: lanthanide nitrate (CASRN 35099-99-1), lanthanum acetate (CASRN 917-70-4), lanthanum bromide (CASRN 13536-79-3), lanthanum chloride hexahydrate (CASRN 17272-45-6), lanthanum chloride heptahydrate (CASRN 10025-84-0), lanthanum chloride (CASRN 10099-58-8), lanthanum nitrate hexahydrate (CASRN 10277-43-7), lanthanum nitrate (CASRN 10099-59-9), and lanthanum sulfate (CASRN 10099-60-2). 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 values: American Conference of Governmental Industrial Hygienists (ACGIH), American Industrial Hygiene Association (AIHA), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), International Agency for Research in Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV), OECD International Uniform Chemical Information Database (IUCLID), OECD Screening Information Data Sets (SIDS), Occupational Safety and Health Administration (OSHA), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA HPV, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, World Health Organization (WHO), Department of Energy

(DOE) Protective Action Criteria (PAC), U.S. Army Public Health Command (APHC) air-Military Exposure Guideline (air-MEG), and Defense Technical Information Center (DTIC).

Toxicity data were not located for lanthanum bromide or lanthanum sulfate; thus, these compounds are not included in the "Introduction" section or considered further in this review.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide overviews of the relevant noncancer and cancer databases, respectively, for lanthanum and 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 Lanthanum (CASRN 7439-91-0)							
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)							
Short-term	10 (sex not specified); Wistar rat; diet; 0, 75, 150 mg $LaCl_3 \cdot 6H_2O$/kg; 18 d	0, 2.6, 5.17 mg La/kg-d	Significant increase in serum ALP and ALT.	NDr	2.6	He et al. (2003)	PR: Liver weight and histopathology were not examined.
Short-term	10 M/10 F; Slc:Wistar rat; gavage; 0, 40, 200, 1,000 mg $LaCl_3 \cdot 7H_2O$/kg-d; daily for 28 d	0, 15, 74.8, 374 mg La/kg-d	Increased incidence of lung lesions (granulation and giant cell appearance) in males.	15	74.8	Ogawa (1992) (Japanese with English abstract and tables)	PR
Subchronic	30 M/dose; ICR mouse; gavage; 0, 2, 5, 10 mg $LaCl_3$/kg-d; daily for 90 d	0, 1, 3, 5.7 mg La/kg-d	Renal vein congestion and serum chemistry changes (increased creatinine; decreased BUN and uric acid) were reported.	NDr	NDr	Zhao et al. (2013)	PR: Due to poor reporting and unreliable statistical results, effect levels could not be identified.
Subchronic	10 M/10 F; S-D rat; gavage; 0, 1.5, 6.0, 24.0, 144.0 mg $La(NO_3)_3$/kg-d; daily for 90 d	0, 0.64, 2.6, 10.3, 61.6 mg La/kg-d	Significant decrease in body weight in male rats, serum ALT, AST in female rats.	10.3	61.6	Fang et al. (2018)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)

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]
Chronic	15 M/dose; Wistar rat; gavage; 0, 0.1, 2, 40 mg $LaCl_3$/kg-d; 5 mo (d/wk of treatment not reported)	0, 0.06, 1, 23 mg La/kg-d	Significantly increased escape latency in Morris water maze.	1	23	Feng et al. (2006b)	PR: Only neurotoxicity endpoints were examined.
Chronic	15 M/15 F; Wistar rat; gavage; 0, 0.1, 0.2, 2.0, 10.0, 20.0 mg $La(NO_3)_3$/kg-d; 6 d/wk for 6 mo	0, 0.036, 0.073, 0.73, 3.63, 7.26 mg La/kg-d	Hepatic lesions (turbulent arrangements of hepatocyte cords and infiltration of inflammatory cells in the portal area) and significant increase in ALP. Decreased body-weight gain was observed at 7.26 mg La/kg-d, but the magnitude of change in absolute body weight is not known.	3.63	7.26	Chen et al. (2003)	PR: Only liver endpoints were examined.
Chronic	10 M/dose; Wistar rat; gavage; 0, 2.0 mg $La(NO_3)_3$/kg-d; 6 mo (d/wk of treatment not reported)	0, 0.85 mg La/kg-d	Changes in bone composition and mineral content indicative of retarded bone maturation.	NDr	NDr	Huang et al. (2006)	PR: Effect levels were not identified due to the lack of information on biological significance of the observed changes.

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)

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]
Developmental (premating, gestational, and postnatal exposure)	7−12 litters/dose; Swiss-Webster mouse; drinking water; parents exposed to $LaCl_3 \cdot 7H_2O$ (0, 125, 250, 500 mg/L); from 14 d before mating through mating, gestation, lactation, until PND 60	Dams: ~0, 33.0, 66.1, 132 mg $LaCl_3 \cdot 7H_2O$/kg-d (~0, 12.4, 24.7, 49.4 mg La/kg-d) Pups: ~0, 41.9, 83.8, 168 mg $LaCl_3 \cdot 7H_2O$/kg-d (~0, 15.7, 31.3, 62.7 mg La/kg-d)	Pup body weight decreased at the mid and high dose. Swimming behavior was delayed at the mid and high dose, but these results were reported inconsistently in the publication. At the low and mid doses, but not the high dose, delays in eye opening and ear opening, as well as behavioral alterations in the touch and visual placing response tests were observed.	NDr 15.7 (Pups)	NDr 31.3 (Pups)	Briner et al. (2000) (Water consumption was not measured.)	PR: Due to the poor reporting and uncertainty regarding the relationship of the effects to treatment, effect levels were not identified.
Developmental (gestational and postnatal exposure)	8 litters/dose, ~4 M/4 F/litter; Wistar rat; drinking water; $LaCl_3$ at concentrations of 0 or 0.25%; GD 7 to PND 21	Dams: 0, 407.1 mg $LaCl_3$/kg-d (0, 230.6 mg La/kg-d)	Impaired olfactory function (measured by buried food pellet and olfaction maze tests) and ultrastructural changes in the olfactory epithelium (enlarged olfactory receptor neuron knobs, increased number of detached knobs, decreased number of cilia).	NDr	230.6	Hao et al. (2012) (Water consumption and maternal body weight were not measured.)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)

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]
Developmental (gestational and postnatal exposure)	8 litters/dose, 4−5 M/4−5 F/litter; Wistar rat; offspring exposed to $LaCl_3$ in utero and via lactation (parents via drinking water at concentrations of 0, 0.25, 0.5, or 1%); until PND 21 and then via drinking water for 1 mo	Dams: 0, 407.1, 814, 1,630 mg $LaCl_3$/kg-d (0, 230.6, 461, 923 mg La/kg-d) Pups: 0, 542.9, 1,090, 2,170 mg $LaCl_3$/kg-d (0, 307.5, 615, 1,230 mg La/kg-d)	Impaired spatial learning and memory (poor performance in Morris water maze) and ultrastructural changes in the hippocampal synapses.	NDr	230.6 (Dam) 307.5 (Pup)	Zheng et al. (2013) (Water consumption and maternal body weight were not measured.)	PR
Developmental (gestational and postnatal exposure)	~2−3 litters/dose; Wistar rat; offspring exposed to $LaCl_3$ in utero and via lactation (parents via drinking water at concentrations of 0, 0.125, 0.25, 0.5, or 1%); until PND 21 and then via drinking water for 1 mo	Dams: 0, 544.9, 1,042, 1,990, 3,720 mg $LaCl_3$/kg-d (0, 308.6, 590.0, 1,130, 2,100 mg La/kg-d) Pups: 0, 619.0, 1,095, 2,000, 3,620 mg $LaCl_3$/kg-d (0, 350.6, 620.3, 1,130, 2,050 mg La/kg-d)	Impaired spatial learning and memory (poor performance in Morris water maze).	NDr	308.6 (Dam) 350.6 (Pup)	Jin et al. (2017) (Maternal body weight was not measured.)	PR
Developmental (gestational and postnatal exposure)	8 litters/dose; Wistar rat; offspring exposed to $LaCl_3$ via lactation (parents via drinking water at concentrations of 0, 0.125, 0.25, or 0.5%); until PND 21 and then via drinking water for 2 mo	Dams: 0, 203.5, 407.1, 814 mg $LaCl_3$/kg-d (0, 115.3, 230.6, 461 mg La/kg-d) Pups: 0, 271.4, 542.9, 1,090 mg $LaCl_3$/kg-d (0, 153.7, 307.5, 615 mg La/kg-d)	Decreased body weight, impaired spatial learning and memory (poor performance in Morris water maze), and ultrastructural changes in the hippocampal synapses.	NDr	115.3 (Dam) 153.7 (Pup)	Zhang et al. (2017) (Water consumption and maternal body weight were not measured.)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)

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]
Developmental (gestational and postnatal exposure)	10 litters/dose; Wistar rat; offspring exposed to $LaCl_3$ in utero and via lactation (parents via drinking water at concentrations of 0, 0.125, 0.25, or 0.5%); until PND 21 and then via drinking water for 1 mo	Dams: 0, 203.5, 407.1, 814 mg $LaCl_3$/kg-d (0, 115.3, 230.6, 461 mg La/kg-d) Pups: 0, 271.4, 542.9, 1,090 mg $LaCl_3$/kg-d (0, 153.7, 307.5, 615 mg La/kg-d)	Impaired spatial learning and memory (poor performance in Morris water maze) and ultrastructural changes in the hippocampal synapses.	–	115.3 (Dam) 153.7 (Pup)	Zhang et al. (2017) (Water consumption and maternal body weight were not measured.)	PR
Developmental (gestational and postnatal exposure)	15 dams/dose, 4 M/4 F/litter; Wistar rat; offspring exposed to 0, 0.1, 2, or 40 mg $LaCl_3$/kg-d during gestation and lactation (gavage administration to dams) and via gavage from PND 20 until 5 mo of age	0, 0.06, 1, 23 mg La/kg-d	Decreased body weight and neurobehavioral changes (decreased swimming endurance and increased escape latency in the Morris water maze).	1	23	Feng et al. (2006a)	PR
Developmental (gestational and postnatal exposure)	**10 dams/dose, 5 M/litter; Wistar rat; offspring exposed to $LaCl_3$ during gestation and lactation (gavage administration to dams) and via gavage (0, 0.1, 2, or 40 mg $LaCl_3$/kg-d) from PND 21 until 6 mo of age**	**0, 0.06, 1, 23 mg La/kg-d**	**Impaired performance in the Morris water maze (increased general path length, decreased preference for target quadrant) and decreased numbers of pyramidal cells in CA3 region of hippocampus.**	**0.06**	**1**	**He et al. (2008)**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)

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]
Developmental (postnatal exposure)	~4 M/4 F/litter, 8 litters/dose; Wistar rat; offspring exposed to $LaCl_3$ via lactation (parents via drinking water at concentrations of 0, 0.25, 0.5, or 1%) until PND 21 and then via drinking water for 1 mo	Dams: 0, 407.1, 814, 1,630 mg $LaCl_3$/kg-d (0, 230.6, 461, 923 mg La/kg-d) Pups: 0, 542.9, 1,090, 2,170 mg $LaCl_3$/kg-d (0, 307.5, 615, 1,230 mg La/kg-d)	Impaired spatial learning and memory (poor performance in Morris water maze) and ultrastructural changes in the hippocampal synapses.	NDr	230.6 (Dam) 307.5 (Pup)	Yang et al. (2009) (Water consumption and maternal body weight were not measured.)	PR
Developmental (postnatal exposure)	~4 M/4 F/litter, 8 litters/dose; Wistar rat; offspring exposed to $LaCl_3$ via lactation (parents via drinking water at concentrations of 0, 0.25, 0.5, or 1%) from birth until PND 21 and then via drinking water for 1 mo	Dams: 0, 407.1, 814, 1,630 mg $LaCl_3$/kg-d (0, 230.6, 461, 923 mg La/kg-d) Pups: 0, 542.9, 1,090, 2,170 mg $LaCl_3$/kg-d (0, 307.5, 615, 1,230 mg La/kg-d)	Reduced levels of Nissl bodies (a decrease indicates neural degeneration) and ultrastructural changes (chromatin condensation and nuclear fragmentation) in the hippocampal neurons.	NDr	230.6 (Dam) 307.5 (Pup)	Yang et al. (2013) (Water consumption and maternal body weight were not measured.)	PR
Developmental (postnatal exposure)	8/group; Wistar rat; offspring exposed to $LaCl_3$ via lactation (parents via drinking water at concentrations of 0, 0.25, 0.5, or 1%) from birth until PND 21 and then via drinking water for 2 mo	Dams: 0, 407.1, 814, or 1,630 mg $LaCl_3$/kg-d (0, 230.6, 461, 923 mg La/kg-d) Pups: 0, 542.9, 1,090, 2,170 mg $LaCl_3$/kg-d (0, 307.5, 615, 1,230 mg La/kg-d)	Dose-related impairments of spatial learning and memory assessed by Morris water maze, and alterations in morphology of the hippocampal synapses.	NDr	230.6 (Dam) 307.5 (Pup)	Liu et al. (2014) (Water consumption and maternal body weight were not measured.)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Soluble Lanthanum (CASRN 7439-91-0)							
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]**
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 ADDs (mg La/kg-day) for oral noncancer effects.
[c]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; F = female(s); GD = gestation day; La = lanthanum; $LaCl_3$ = lanthanum(III) chloride; $LaCl_3 \cdot 6H_2O$ = lanthanum(III) chloride hexahydrate; $LaCl_3 \cdot 7H_2O$ = lanthanum(III) chloride heptahydrate; $La(NO_3)_3$ = lanthanum(III) nitrate; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; PND = postnatal day; S-D = Sprague Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for Soluble Lanthanum (CASRN 7439-91-0)							
Category	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**LOAEL**	**Reference**	**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							

LOAEL = lowest-observed-adverse-effect level; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

The pulmonary toxicity of inhaled lanthanides, in general, has been the subject of debate, especially regarding the relative contributions of radioactive contaminants versus stable elements in the development of progressive pulmonary interstitial fibrosis (Beliles, 1994; Haley, 1991). Although it is known that stable rare earth compounds can produce a static, foreign-body-type lesion consistent with benign pneumoconiosis, there is uncertainty whether they 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 inhalation toxicity data on stable rare earths consist of a few inhalation and intratracheal studies, on 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). 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 indicative of 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.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure to lanthanum chloride (or its hepta- or hexahydrate) were investigated in an 18-day rat study (He et al., 2003), a 4-week rat study published in Japanese (Ogawa, 1992), a 3-month mouse study examining renal endpoints (Zhao et al., 2013), a 5-month rat study examining neurotoxicity endpoints (Feng et al., 2006b), and 11 developmental studies examining neurotoxicity or olfactory effects, in rats or mice exposed during gestation, lactation, and/or postnatally (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Hao et al., 2012; Yang et al., 2009; He et al., 2008; Feng et al., 2006a; Briner et al., 2000). Gavage administration was used in five studies (Zhao et al., 2013; He et al., 2008; Feng et al., 2006a; Feng et al., 2006b; Ogawa, 1992) and one study used dietary administration (He et al., 2003) while the remaining studies (Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Hao et al., 2012; Yang et al., 2009; Briner et al., 2000) used drinking water administration. The effects of oral exposure to lanthanum nitrate were investigated in one 90-day gavage study (Fang et al., 2018), and two 6-month rat gavage studies examining liver (Chen et al., 2003) and bone (Huang et al., 2006) endpoints.

Short-Term-Duration Studies

He et al. (2003)

Groups of 10 Wistar rats (sex not specified) received dietary concentrations of 0, 75, or 150 mg lanthanum chloride hexahydrate ($LaCl_3 \cdot 6H_2O$; purity 99%)/kg (0, 2.6, or 5.17 mg La/kg-day, calculated using body-weight and food-consumption data from the study) for 18 days (He et al., 2003). Food intake was assessed daily, and body weight was measured every 3 days. At the end of exposure, blood samples were collected and analyzed for serum total cholesterol, total protein, albumin, total triglycerides, glucose, creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). At sacrifice, the thymus and spleen were weighed. Body weights did not differ significantly from controls in either exposed group. At 5.17 mg La/kg-day, statistically significantly increased ALP (57% higher than controls) and ALT (134% higher) were seen; there

were no effects on other serum chemistry parameters, including BUN and creatinine (see Table B-1). At 2.6 mg La/kg-day, a significant 82% increase in ALT was seen (see Table B-1). A nonsignificant 20% increase in thymus weight was observed in high-dose rats; spleen weight was not affected. A lowest-observed-adverse-effect level (LOAEL) of 2.6 mg La/kg-day is identified for these data based on a significant increase in serum ALT; note, however, that liver weights and histopathology were not assessed, so the biological significance of the serum chemistry changes is uncertain. A no-observed-adverse-effect level (NOAEL) could not be identified.

Ogawa (1992)

In a 28-day gavage study of lanthanum chloride in rats published in Japanese with an English abstract and tables, lanthanum chloride heptahydrate ($LaCl_3 \cdot 7H_2O$; purity 99.9%) was administered by daily gavage to 10 Slc:Wistar rats/sex/dose. The vehicle used in this study was potentially a 5% glucose solution based on a similar study conducted by this author (Ogawa, 1992). Doses were 0, 40, 200, or 1,000 mg $LaCl_3 \cdot 7H_2O$/kg-day (0, 15, 74.8, or 374 mg La/kg-day). A pair-fed control group was given the same diet intake as the high-dose group. Additional control and high-dose groups of the same size were treated for 28 days, and then observed untreated for an additional 14 days.

Evaluations were not detailed in the English abstract (Ogawa, 1992). Based on other 28-day studies of lanthanide elements by the same investigator (Ogawa et al., 1995; Ogawa et al., 1992), and the tabulated and graphical results, investigations included observations for mortality and clinical signs, measurement of body weights and food consumption, urinalysis, hematology, serum chemistry, gross necropsy, selected organ weights, and comprehensive histopathology on half of the animals per sex, per group. The study author measured lanthanum and iron concentrations in the liver, kidney, and spleen, as well as in the bone. The study author also measured the bone concentrations of barium, strontium, and zinc. Statistical assessments were not described in the abstract or noted in the tables and figures.

Based on visual inspection of data presented graphically, body weights of the males exposed to ≥74.8 mg La/kg-day were lower than untreated controls throughout the study, reaching a decrease of ~10% at the end of the treatment period that continued at the same magnitude through the recovery period (Ogawa, 1992). There was no apparent effect on female body weight. Similarly, food intake was decreased relative to untreated controls in the mid- and high-dose males throughout the treatment period, but was not affected in females. Body weight in the pair-fed controls mirrored that of the mid- and high-dose males. Hematology data reported in graphs or tables were limited to eosinocyte ratios of the differential white blood cell (WBC) count; these were significantly increased relative to untreated controls in males at all doses and in females exposed to 74.8 mg La/kg-day (an increase in high-dose females was not statistically significant due to substantial variability in individual values). Eosinocyte ratios in pair-fed controls did not differ from untreated controls.

Serum chemistry and histopathology findings are reported in Tables B-2 and B-3. Compared with untreated controls, the exposed animals exhibited significantly lower total protein at the high dose; total protein was also decreased in the pair-fed controls (Ogawa, 1992). In addition, high-dose rats of both sexes exhibited statistically significant increases in both ALT and AST compared with both untreated and pair-fed controls. No statistically significant changes in BUN or serum creatinine were observed in either sex when compared with untreated

controls. At the high dose, BUN in both sexes and creatinine in females were increased relative to pair-fed controls, but these values were lower than in untreated controls. Female rats exhibited statistically significant and dose-related increases in serum uric acid relative to both untreated and pair-fed controls; no significant changes were seen in males relative to either control group. Female rats exhibited significantly lower serum cholinesterase at the mid and high doses compared with untreated controls, and at the high dose when compared with pair-fed controls. Organ-weight information was not reported in the abstract or English tables.

The study showed dose-related increases in tissue concentrations of lanthanum; concentrations were highest in the liver (~2−5 µg/g dry weight based on data shown graphically), followed by kidney (≤1 µg/g), and bone and spleen (~<0.5 µg/g) (Ogawa, 1992). Lanthanum intake at the highest dose resulted in significantly decreased iron concentrations in the liver (high-dose males and females), kidney (high-dose males), and spleen (high-dose females and mid- and high-dose males). In addition, lanthanum exposure decreased the concentrations of barium and strontium, while increasing zinc content in the bone. Histopathology findings were reported for the lung and stomach; the report abstract stated that there were no findings in the liver, and there were presumably no noteworthy findings in the kidneys or other organs. Significantly increased incidences of granulation and giant cell appearance in the lung were reported for males exposed to ≥74.8 mg La/kg-day and females exposed to 74.8 mg La/kg-day, but not 374 mg La/kg-day (this lesion was seen in 1/5 high-dose females but the increase was not significant; see Table B-3). High-dose females exhibited a significant increase in the incidence of alveolar wall thickening, which could have obscured other lesions such as granulation and giant cell appearance in this group. Eosinocyte infiltration was also observed in the lungs of mid- and high-dose males and in mid-dose females, but not in the control animals or in the control or dosed recovery groups. In addition, significantly increased incidences of lesions in the forestomach, glandular stomach, and submucosa were observed in high-dose rats of both sexes (see Table B-3): these included hyperkeratosis of the forestomach (females only), dilatation of the acinus in the glandular stomach (males only), swelling of the glandular stomach epithelium (females only), and eosinocyte infiltration of the submucosa (both sexes). Forestomach hyperkeratosis and erosion of the glandular stomach were also seen in high-dose males, but the incidences (2/5 and 3/5, respectively) were not statistically significantly increased over the control incidence (0/5).

Based on the information provided in the English abstract, tables, and figures, a LOAEL of 74.8 mg La/kg-day is identified based on increased incidences of pulmonary lesions (granulation, giant cell appearance, and eosinocyte infiltration). The NOAEL is 15 mg La/kg-day.

Subchronic-Duration Studies

Zhao et al. (2013)

Lanthanum chloride (analytical grade, purity not reported) was administered in distilled water by gavage to male ICR mice for 90 consecutive days in a study comparing renal effects of lanthanum, cerium, and neodymium. The number of animals per group is uncertain; the study authors reported n = 30/group, but also reported that 150 mice were randomly distributed among 10 groups (resulting in n = 15/group), and group sizes in the "Results" section of the study report were given as n = 5/group. Doses were reported as 0, 2, 5, or 10 mg $LaCl_3$/kg-day (0, 1, 3, or

5.7 mg La/kg-day).[2] Mortality and clinical signs were noted daily, and body weight was measured at the end of treatment. Blood collected at sacrifice was analyzed for serum markers of kidney function (uric acid, BUN, creatinine, calcium, and phosphorus). No urine analyses were performed. Kidneys were weighed and examined microscopically, and the lanthanum content was analyzed. Markers of oxidative stress, antioxidant enzyme activity and gene expression, and antioxidant levels in the kidney were measured. Statistical analyses consisted of unpaired Student's *t*-tests, without correction for multiple comparisons.

The study report presented no information on mortality or clinical signs. Significant, dose-related decreases in body-weight gain were observed at all doses of lanthanum, but the study authors did not report absolute body weights. Based on visual inspection of data presented graphically, body-weight gains in treated mice were 10−30% lower than controls. Relative kidney weights were increased in a dose-dependent fashion, likely due in large part to the decreases in overall body-weight gain; the magnitude of change from control was also ~10−30% in the treated groups. Exposure to lanthanum chloride also resulted in a dose-related increase in serum creatinine and dose-related decreases in serum uric acid, BUN, calcium, and phosphorus (see Table B-4). The study authors reported that these changes were statistically significantly different from controls at all doses. However, efforts to reproduce the statistical *t*-tests using data reported in the publication indicated that the changes in creatinine, BUN, calcium, and phosphorus were not significant ($p \geq 0.09$) at the low dose, even without correction for multiple comparisons, raising doubt about the reliability of the statistics reported in the publication. The renal lesions, which consisted of congestion of the vein and mesenchyme blood vessel and inflammatory cell infiltration, were reportedly observed at all doses of lanthanum chloride, but neither the incidences nor severity of these lesions was reported. The study authors reported that more serious renal lesions, including tubular necrosis, were seen in mice exposed to cerium and neodymium. All markers of oxidative stress exhibited dose-related increases with lanthanum treatment, along with accompanying decreases in antioxidant enzyme activities, protein levels, and gene expression.

Data from this study suggest the possibility of lanthanum-induced effects on the kidney, but the information provided is not sufficiently reliable to identify a NOAEL or LOAEL due to poor reporting (neither incidence nor severity of renal lesions were reported) and unreliable statistical results (some test results were demonstrably incorrect, and the overall approach failed to account for multiple comparisons).

Zhao et al. (2013)

Lanthanum nitrate ($La[NO_3]_3$; purity 98%) was administered once daily in distilled water by gavage to 5-week-old Sprague-Dawley (S-D) rats (10/dose/sex) at dose levels of 0, 1.5. 6.0, 24.0, or 144.0 mg/kg-day (0, 0.64, 2.6, 10.3 or 61.6 mg La/kg-day) for 90 days. Five male and five female rats from the highest dose group and control group (5/dose/sex) were observed in a 4-week recovery period. Mortality and clinical signs were noted daily, and body weight was measured weekly during the treatment and at the end of treatment. Food consumption of each rat was also measured weekly.

At the end of the study, urine samples were collected overnight and analyzed for leukocytes, nitrite, urobilinogen, bilirubin, protein, glucose, specific gravity, pH, and occult

[2]Corresponding lanthanum doses were calculated using the ratio of molecular weights ($La:LaCl_3 = 138.91:245.27$).

blood. Rats that fasted overnight were anesthetized, and blood was collected and subjected to comprehensive hematological examination and serum biochemistry evaluation. All animals received a complete necropsy, and the adrenals, brain, heart, kidneys, liver, spleen, thymus, testes, and epididymis were weighted, and then subjected to histopathological examination. Statistical analysis for differences between the treated and control groups used analysis of variance (ANOVA) followed by Dunnett's test. Urinalysis and histopathological data were analyzed using the Mann-Whitney U test.

The study authors reported no mortality or clinical signs at the end of study. Statistically significant decreases in body weight (data were only reported in a graph) were observed in male and female rats in the highest dose (61.6 mg La/kg-day) group, which were accompanied by significant decreases in food intake. Based on a visual inspection of data presented graphically, body weights of only male rats in the highest dose group decreased more than 10% compared to the controls. In the male rats treated with 61.6 mg La/kg-day, the organ weights of the liver, spleen, kidney, heart, and thymus were significantly decreased (see Table B-5), and the relative brain and epididymis weights significantly increased compared to those in the controls. Most of the hematological parameters were not significantly different between treated groups and the control; however, significant differences were observed in some parameters, including an increase in prothrombin time (PT) in male rats of the 0.64-mg La/kg-day dose group, and a decrease in WBC and reticulocyte count (RET) in males of the 61.6-mg La/kg-day dose group. There were dose-related decreases in blood triglyceride in males at dose levels ≥10.3 mg La/kg-day. Exposure to 61.6 mg La/kg-day resulted in an increase in phosphorous in male rats, and statistically significant increases in ALT, AST, glucose, urea, creatinine, and calcium in female rats (see Table B-6). Urinalysis indicated no significant changes in any of the nine urinary parameters between treated groups and controls (data not shown). Most of the histopathological findings in all treated groups were comparable with those in the controls, except of some observations in the heart, liver, kidneys, reproductive organs, and lungs, which the study authors considered spontaneous background changes in S-D rats. Based on the significant decreases in body weight in the male rats and increases in serum ALT and AST in females, a LOAEL of 61.6 mg La/kg-day and a NOAEL 10.3 mg La/kg-day are identified.

Chronic-Duration Studies

Feng et al. (2006b)

A 5-month study of neurotoxicity endpoints was conducted in 4-week-old male Wistar rats exposed to lanthanum chloride (purity 99.99%; vehicle not reported) (Feng et al., 2006b). Groups of 15 rats/dose received daily gavage doses of 0, 0.1, 2, or 40 mg $LaCl_3$/kg-day (0, 0.06, 1, or 23 mg La/kg-day). At 6 months of age, groups of 12 animals/dose were subjected to testing for escape latency (no other metrics were assessed) in the Morris water maze every day for 8 consecutive days (four trials per day). Groups of three rats/dose were sacrificed after behavioral testing, and their brains were examined by synchrotron radiation X-ray fluorescence (SRXRF) analysis to map the distributions of calcium, iron, and zinc; additional brain samples were analyzed for lanthanum using inductively coupled plasma-mass spectrometry (ICP-MS). Additional groups of 10 rats/dose were sacrificed for measurement of monoamine neurotransmitters and acetylcholinesterase (AChE) activity in the brain. Statistical analysis for differences from control employed ANOVA followed by the least significant difference (LSD) test.

Rats exposed to 23 mg La/kg-day exhibited significantly increased escape latency in the Morris water maze on Days 2, 3, and 4 of testing; no other statistically significant changes in escape latency were observed (Feng et al., 2006b). Controls and low-dose animals learned the maze within 3 or 4 days of testing, reaching an average escape latency of ~20 seconds that remained relatively constant through the remainder of testing, while high-dose rats took longer to learn the maze, not reaching an average 20-second latency until Day 8 of testing. The rats in the high-dose group also had lanthanum levels in the brain that were above detection limit; levels ranged from 0.014 µg/g dry weight in the hippocampus to 0.039 µg/g in the cerebral cortex. Lanthanum exposure, especially at the highest dose, decreased the concentrations of calcium, iron, and zinc in the brain, and altered the distributions of these elements. In addition, the activity of calcium-ATPase was significantly decreased in the brain at the high dose. Significant decreases in several neurotransmitter levels (dopamine, dihydroxyphenylacetic acid, 5-hydroxytryptamine [5-HT], and norepinephrine) were observed at the high dose of lanthanum chloride; 5-HT levels were also decreased at the mid dose (see Table B-7). However, the functional significance of the change in 5-HT at the mid dose in and of itself is unclear. Levels of the neurotransmitters, homovanillic acid and 5-hydroxyindoleacetic acid, were not significantly altered by lanthanum treatment. Brain AChE activity was significantly decreased and acetylcholine content increased at the low dose, but not at higher doses.

The delayed learning exhibited by rats exposed to lanthanum chloride may be related to other changes, such as decreased calcium and zinc in the brain. Perturbations of neuronal calcium homeostasis in the brain can have neurological effects, and decreased zinc in the hippocampus (which is involved in spatial memory and navigation) is known to impair spatial memory in rats (Feng et al., 2006b). Furthermore, decreases in neurotransmitter levels may also be involved in memory impairment by lanthanum chloride. Several monoamine neurotransmitters, including norepinephrine, dopamine, and 5-HT are reduced with age and/or shown to impair working memory (Feng et al., 2006b). Finally, decreased iron as seen in the exposed rats may have led to the decreases in monoamine neurotransmitters, because iron is a cofactor for many enzymes involved in the production of these neurotransmitters (Feng et al., 2006b).

Based on the significant delay in learning at the high dose and decreased multiple neurotransmitter levels (dopamine, dihydroxyphenylacetic acid, 5-HT, and norepinephrine) at the same dose, this study indicates a LOAEL of 23 mg La/kg-day for neurobehavioral effects; the NOAEL is 1 mg La/kg-day.

Chen et al. (2003)

Toxicity of lanthanum nitrate to the rat liver was evaluated in a 6-month study (Chen et al., 2003). Groups of Wistar rats (15/sex/dose) received lanthanum nitrate (purity 99.9%, in physiological saline) at doses of 0, 0.1, 0.2, 2.0, 10.0, or 20.0 mg $La(NO_3)_3$/kg-day (0, 0.036, 0.073, 0.73, 3.63, or 7.26 mg La/kg-day) by gavage 6 days/week for 6 months. At the end of exposure, the animals were sacrificed and blood was collected for analysis of serum chemistry (AST, ALT, γ-glutamyl transferase [GGT], and ALP). Relative liver weight was measured, and the liver was examined by light and transmission electron microscopy (TEM). Oxidative stress indicators (superoxide dismutase [SOD], glutathione peroxidase, and malondialdehyde [MDA]) and lanthanum content in the liver were measured. Statistical analysis consisted of Student's *t*-tests.

Body-weight gain was significantly lower than controls in male (but not female) rats exposed to 7.26 mg La/kg-day (absolute body weight and body-weight gain data not shown). No significant change in relative liver weight (and <10%) was observed in males exposed to lanthanum nitrate (Chen et al., 2003) (note that the study authors reported a significant increase in relative liver weight in males exposed to 7.26 mg La/kg-day; however, efforts to reproduce the statistical *t*-tests using data reported in the publication indicated that the liver-weight changes in male rats were not significant at any dose, calling into question the reliability of the statistics reported in the publication). A significant decrease in relative liver weight was reported in female rats exposed to 0.036 mg La/kg-day, but not other treatment groups. In male rats, but not female rats, significant increases (confirmed by *t*-tests performed for this review) in serum ALP were noted at 0.036, 0.073, 0.73, and 7.26 (but not 3.63) mg La/kg-day, but there were no clear dose-dependent changes at dose levels ≤3.63 mg La/kg-day; at the highest dose, serum ALP was more than doubled (see Table B-8). No other serum chemistry changes were observed. Oxidative stress markers were significantly increased at 0.036 and 0.073 mg La/kg-day, but not higher doses, of lanthanum nitrate; the significance of this finding is uncertain. The lanthanum content of the liver increased with dose. Lesions were observed in the livers of animals exposed to 7.26 mg La/kg-day (the study authors did not specify which sex[es] were affected, and incidences and severity were not reported) but not at lower doses or in controls; the lesions consisted of "turbulent arrangements of hepatocyte cords" and infiltration of inflammatory cells in the portal area. Glycogen depletion was also observed at the highest dose. TEM examination of the hepatocytes showed numerous lysosomes containing electron-dense particles clustered around bile canaliculi and perinuclear cytoplasm, as well as increased numbers of fat droplets, especially at the highest dose. A LOAEL of 7.26 mg La/kg-day is identified for this study based on hepatic lesions and a doubling of serum ALP. Decreased body-weight gain was also observed at this dose, but the magnitude of change in absolute body weight is not known. The NOAEL is 3.63 mg La/kg-day.

Huang et al. (2006)

A study of lanthanum nitrate (purity not reported) effects on bone composition and structure was conducted in male Wistar rats (10/dose) exposed by gavage for 6 months to doses of 0 or 2.0 mg $La(NO_3)_3$/kg-day (0 or 0.85 mg La/kg-day) (Huang et al., 2006). Vehicle was not reported. At sacrifice at the end of exposure, both femurs were removed for analysis of lanthanum, calcium, and phosphorus content; bone mineral crystal size, orientation, thickness and arrangement, calcium coordination in bone mineral, and bone mineral dissolution kinetics were also examined. Data were analyzed by ANOVA and Scheffe's test.

Exposure to lanthanum resulted in statistically significant 11.6 and 16.7% decreases in calcium and phosphorus content of the bone, respectively, a 10% decrease in the ratio of bone mineral to matrix (relative to controls), and in the ratio of bone mineral to matrix (relative to controls), as well as a significant 40.9% increase in carbonate content (see Table B-9) (Huang et al., 2006). Increased levels of labile carbonate and acidic phosphate were observed, and the mean thickness of mineral crystals was decreased in the exposed rats. These changes make bone mineral easier to dissolve, and studies of dissolution kinetics showed more rapid dissolution of bone mineral from lanthanum nitrate-treated rats compared with controls. The study authors considered these changes in bone composition and mineral content to be indicative of retarded bone maturation (Huang et al., 2006). However, in the absence of information on the functional significance of altered bone composition and dissolution kinetics, the biological significance of

this finding is uncertain and effect levels are not identified. Thus, neither a NOAEL nor a LOAEL could be identified.

Developmental Studies

Briner et al. (2000)

A study of neurodevelopmental effects was conducted in Swiss-Webster mice exposed to lanthanum chloride heptahydrate in drinking water (Briner et al., 2000). Female mice were exposed for 14 days before being mated to untreated males, and exposure continued through mating, gestation, and lactation. After weaning, the pups were exposed to the same concentrations as their mothers until sacrifice. Exposure concentrations were 0, 125, 250, or 500 mg $LaCl_3 \cdot 7H_2O$/L. Water consumption was not measured, but based on default assumptions for water intake and body weight, maternal doses of ~0, 33.0, 66.1, or 132 mg $LaCl_3 \cdot 7H_2O$/kg-day (0, 12.4, 24.7, or 49.4 mg La/kg-day) were estimated, and pup doses of ~41.9, 83.8, or 168 mg $LaCl_3 \cdot 7H_2O$/kg-day (0, 15.7, 31.3, or 62.7 mg La/kg-day) were estimated. The pups were evaluated for eye and ear opening, as well as swimming ability every day between Postnatal Days (PNDs) 4 and 20. Pup body weights were recorded on PNDs 4, 8, 12, 16, and 20. The pups were evaluated in a functional observational battery (FOB; excluding the open field component, which the study authors reported was not affected in a pilot study) between PNDs 30 and 32. At sacrifice on PNDs 59 or 60, the pups' brains were weighed and analyzed for lanthanum, lipid, and protein content. Statistical analysis of continuous data employed ANOVA with unspecified follow-up testing, and analysis of categorical data employed the χ^2 test. The litter was the unit of statistical analysis.

The study authors stated that lanthanum chloride exposure did not affect maternal health (evaluations were not reported) (Briner et al., 2000). Litter size, sex ratio, and pup mortality did not differ significantly between exposed and control mice; however, the study authors noted that the litter size was slightly smaller at the high dose (7.6 ± 2.5 pups) compared with controls (8.0 ± 3.3). Pups in the mid- and high-dose groups exhibited lower body-weight gain, although body weights did not differ significantly from controls. Based on data presented graphically, body weights of these two groups appeared to be >5% lower than controls on PND 20. The percentage of pups with eyes open at PND 14 was significantly lower than controls at the low and mid doses (~60 and ~30%, respectively, compared with ~80% in controls), but not at the high dose (~90%); there were no differences at other time points for all doses. A similar phenomenon was seen with the percentage of pups with ears open on PND 13 (~80, 44, 28, and 84% in control, low-, mid-, and high-dose groups, respectively); the percentages did not differ at other time points. None of the pups in the mid-dose group were walking by PNDs 5 or 6, compared with ~65% in the control and 25−50% in the other exposure groups; at later time points, the groups did not differ. Results of assessments of swimming behavior were reported inconsistently in the publication. In the graph presenting the results, the legend indicated that significant delays in swimming behavior were seen in the low- and mid-dose groups, but not in the high-dose group; in contrast, the text and the figure caption indicated that the significant delays were seen in the mid- and high-dose groups. Thus, it appears likely that the figure legend is in error, and that the swimming delays occurred at all but the lowest dose. In the FOB assessment, only the touch response and visual placing response tests were altered by treatment (Briner et al., 2000). In both tests, the low- and mid-dose groups exhibited significantly different behaviors compared with controls, while the high-dose group did not. A significant decrease in absolute (but not relative) brain weight (data shown graphically) was observed in the high-dose

pups. Brain levels of protein, lipids, and lanthanum did not differ significantly between the exposed and control animals.

In summary, swimming behavior was delayed at the mid and high doses, although these results were reported inconsistently. At the low and mid doses, but not the high dose, delays in eye and ear opening were seen, as well as behavioral alterations in the touch and visual placing response tests. However, the lack of effect at the highest dose raises uncertainty regarding the relationship of these changes to treatment. The study authors suggested two possible explanations for the lack of response at the high dose. The first was that lanthanum exposure resulted in the death of embryos susceptible to lanthanum toxicity before birth. However, the difference in litter size was not statistically significant (7.6 vs. 8.0). The second explanation, based on in vitro studies showing that lanthanum can promote neurite formation, was that the higher dose of lanthanum promoted pup growth, sped maturation, and resulted in developmental milestones and behavior more resembling that of the controls. Because the study authors did not measure water intake, it is also possible that the high-dose animals consumed less water than other groups, potentially leading to a lower lanthanum dose than either of the other exposure groups. It is also possible that the observed changes were not related to treatment. A LOAEL of 31.3 mg La/kg-day and NOAEL of 15.7 mg La/kg-day are identified based on the decreases in body weight and delayed swimming behavior in pups.

Hao et al. (2012)

Groups of eight pregnant Wistar rats were exposed via drinking water to lanthanum chloride (purity 99.9%) at a concentration of 0.25% from Gestation Day (GD) 7 to PND 21 (Hao et al., 2012). Water consumption was not measured. Based on default water intake and body weight, the maternal doses were estimated to be approximately 0 and 407.1 mg $LaCl_3$/kg-day, or 0 and 230.6 mg La/kg-day (U.S. EPA, 1988). Maternal body weight, gestation length, parturition success, litter size, and number of viable pups were recorded. The litters were culled on PNDs 4 to 8/litter (4 males and 4 females when possible). Between PNDs 23−28, the pups were tested for olfactory function in the buried food pellet and olfactory maze tests. In the buried food pellet test, pups were placed on a food-restricted diet for 3 days before and during a 3-day testing period. During testing, the rats were placed in a cage containing a food pellet under a 5-cm thickness of bedding material, and the time required for the rat to find the food pellet was recorded. In the olfaction maze test, also conducted during the food-restricted period, food was placed in a hidden location at a random corner in a maze to which the rats had become familiarized, and the time between when the rat was placed at the center of the maze and when the food was located was recorded. After olfactory testing was completed, the pups were sacrificed for analysis of body, brain, and olfactory bulb weights, and the olfactory epithelia were examined by TEM. Lanthanum content of the olfactory bulb was measured. Finally, the olfactory epithelium was analyzed for protein and messenger ribonucleic acid (mRNA) levels of olfactory marker protein and βIII-tubulin, markers of olfactory maturation. Differences between exposed and control measurements were analyzed by Student's *t*- and χ^2 tests; the unit of statistical analysis was the litter.

There were no significant effects of treatment on gestation or litter parameters, or on pup body, brain, or olfactory bulb weights (Hao et al., 2012). The lanthanum content of the olfactory bulb was significantly increased by exposure (18.5 vs. 2.3 ng/g in controls). In both olfactory tests, a significantly increased latency for detection of food pellets was observed in exposed rats, while latency to find a visible food pellet was not different between the exposed and control rats

(see Table B-10). TEM examination of the olfactory epithelium confirmed treatment-related effects consisting of enlarged olfactory reception neuron knobs, sometimes with irregular shapes, significantly increased numbers of detached knobs, and significantly decreased numbers of cilia. Exposure to lanthanum chloride also resulted in diminished expression of olfactory marker protein and βIII-tubulin. A LOAEL of 230.6 mg La/kg-day is identified from this study based on impaired performance in olfactory testing and ultrastructural changes in the olfactory epithelium at the only dose tested. A NOAEL could not be identified.

Zheng et al. (2013)

In a similar study that included gestational exposure, pregnant Wistar rats (8/dose) were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.25, 0.5, or 1% during pregnancy (details of exposure days not reported) and lactation (Zheng et al., 2013). Groups of 4−5 pups/sex/litter that were exposed during gestation and lactation were subsequently exposed via drinking water at the same concentrations as their mothers for 1 month postweaning. Water consumption and maternal body weight were not measured. The maternal doses were estimated to be 407.1, 814, and 1,630 mg $LaCl_3$/kg-day, or 0, 230.6, 461, and 923 mg La/kg-day; the pup doses were estimated to be 542.9, 1,090, and 2,170 mg $LaCl_3$/kg-day, or 0, 307.5, 615, 1,230 mg La/kg-day for pups.[3] At the end of exposure, the pups were tested in the Morris water maze. After testing, the pups were weighed and then sacrificed for measurement of brain weight, quantification of lanthanum content in the hippocampus, and TEM examination of the hippocampus. Hippocampal protein and mRNA levels of genes involved in the NF-κB signaling pathway were measured. Data analysis consisted of ANOVA for differences among groups followed by Student-Newman-Keuls (SNK) test for multiple comparisons. The litter was the unit of statistical analysis for Morris water maze performance metrics, as well as body and brain weights.

Zheng et al. (2013) and a series of similar studies conducted by the same research group [including Jin et al. (2017); Zhang et al. (2017); Liu et al. (2014); Yang et al. (2013); Yang et al. (2009)] reported the exposure concentrations both as a percentage (without specifying volume/volume [v/v] or weight/volume [w/v]) and as millimolar (mM) concentrations. Because lanthanum chloride is a solid, it is assumed that the drinking water percentages were percent w/v, or g/100 mL. Under this assumption, the concentrations reported as 0.25, 0.5, and 1% are equivalent to concentrations of 2,500, 5,000, or 10,000 mg/L, respectively. The mM concentrations (18, 36, and 72 mM) reported by the study authors correspond to these concentrations only if the molecular weight of lanthanum (not lanthanum chloride) is used. However, throughout the paper, the study authors refer to the concentrations as percent $LaCl_3$. Thus, to calculate doses, the mM concentrations were ignored, and the percentages were assumed to represent g/100 mL as $LaCl_3$.

Significant reductions in pup terminal body weights were observed at all the doses (6.7, 16.4, and 31.5% in low-, mid-, and high-dose groups, respectively; see Table B-11) (Zheng et al., 2013). Absolute, but not relative, brain weights were statistically significantly decreased in the mid- and high-dose groups. Apart from brain and body weights, all results were presented

[3]Using a default estimate of body weight from subchronic-duration studies (0.156 kg) and water intake calculated using an allometric equation (intake in L/day = 0.1 × [body weight in $kg^{0.7377}$]), both from U.S. EPA (1988), the pup doses from drinking water were estimated using a default estimate of body weight from studies of weanling animals (0.0525 kg) and water intake was calculated using the same allometric equation.

graphically. Statistically significant, dose-related impairments of spatial learning and memory were evident from analysis of Morris water maze performance (increased escape latency and total distance traveled, decreased time spent in target quadrant and number of target quadrant crossings). Of these four metrics, the time spent in the target quadrant was significantly different at the mid and high doses, while all others were significant at all doses. Dose-related alterations in synaptic ultrastructure of the hippocampus, consisting of shorter synaptic active zones, thinner postsynaptic density, fewer synaptic vesicles, and uneven curve of the synaptic interfaces, were observed (quantitative results not reported). Treatment with lanthanum chloride also resulted in dose-related reductions in the expression of phosphorylated IκB kinase complex, phosphorylated IκBα, NF-κB, c-fos, c-jun, and brain-derived neurotrophic factor (BDNF) in the hippocampus. A LOAEL of 230.6 mg La/kg-day based on maternal exposure is identified from this study, based on decreases in body weight, impaired spatial learning and memory (poor performance in Morris water maze), and ultrastructural changes in the hippocampal synapses in pups. A NOAEL could not be identified.

Jin et al. (2017)

In another study that included gestational exposure, pregnant Wistar rats (2−3/dose) were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.125, 0.25, 0.5%, or 1% during pregnancy and lactation (3 weeks). The pups were exposed during lactation, and subsequently exposed via drinking water at the same concentrations as their mothers for 1 month postweaning. Because the study authors reported water consumption in dams and pups, the doses were estimated based on the water consumption and default body weight to be 0, 308.6, 590.0, 1,130, and 2,100 mg La/kg-day for dams and 0, 350.6, 620.3, 1,130, and 2,050 mg La/kg-day for pups. At the end of exposure, 20 pups from each dose group were tested in the Morris water maze. After testing, the pups were sacrificed for examination of the hippocampus. Hippocampal protein and mRNA levels of glycogen synthetase, glycogen phosphorylase, lactate dehydrogenase A, monocarboxylate transporter 4, MCT-1, and MCT-2, as well as total lactate dehydrogenase (LDH) activity and lactate contents in the hippocampus were measured. Data analysis consisted of an ANOVA for differences among groups followed by the least significant difference test for multiple comparisons.

Statistically significant, dose-related impairments of spatial learning and memory were evident from analysis of Morris water maze performance (increased escape latency and total distance traveled, decreased time spent in target quadrant and number of target quadrant crossings). All four metrics were significantly different from the controls at all doses. Treatment significantly reduced the mRNA and protein levels of glycogen synthetase, glycogen phosphorylase, lactate dehydrogenase A, monocarboxylate transporter 4, MCT-1, and MCT-2 and decreased the total LDH activity and lactate contents in the hippocampus. A LOAEL of 308.6 mg La/kg-day based on maternal exposure from drinking water is identified from this study, based on decreases in impaired spatial learning and memory (poor performance in Morris water maze) in pups. A NOAEL could not be identified.

Zhang et al. (2017)

In a study that included only lactation exposure, maternal Wistar rats (8/dose) were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.125, 0.25, or 0.5% during lactation (3 weeks). Four pups (sex unknown) were culled in each litter. The pups were exposed during lactation and subsequently exposed via drinking water at the same concentrations as their mothers for 2 months postweaning. Water consumption and maternal

body weight were not measured. The doses were estimated to be 0, 115.3, 230.6, and 461 mg La/kg-day for dams and 0, 153.7, 307.5, and 615 mg La/kg-day for pups. At the end of exposure, 10 pups from each dose group were tested in the Morris water maze. After testing, the pups were weighed and then sacrificed for measurement of brain weight and hippocampus weight, pathological changes, and TEM examination of the hippocampus. Hippocampal protein and mRNA levels of genes involved in the Nrf2/antioxidant response element signaling pathway as well as reactive oxygen species indexes (reactive oxygen species [ROS], malondialdehyde [MDA], glutathione [GSH], catalase, superoxide dismutase [SOD], and glutathione peroxidase [GSH-Px]) were measured. Data analysis consisted of ANOVA for differences among groups followed by SNK test for multiple comparisons.

Significant reductions in pup terminal body weights were observed at all the doses (10.6, 11.7, and 31.5% in low-, mid-, and high-dose groups, respectively; see Table B-12). Absolute, but not relative, brain weights were statistically significantly decreased at all doses. There were no statistically significant changes in absolute and relative hippocampus weight. Apart from brain and body weights, all results were presented graphically. Statistically significant, dose-related impairments of spatial learning and memory were evident from analysis of Morris water maze performance (increased escape latency and total distance traveled, decreased time spent in target quadrant and number of target quadrant crossings). Of these four metrics, escape latency and number of target quadrant crossings were significantly different from the controls at all doses, while time spent in the target quadrant and total distance traveled were significantly different from controls at the mid and high doses. Treatment-related alterations in ultrastructure of the CA1 and CA3 areas of the hippocampus, consisting of pyknosis of the cytoplasm and nucleolus, swollen mitochondria and lysosomes, jagged edges of the nuclear envelope, and increased number of endosomes in the lysosome, were observed (quantitative results not reported). Treatment with lanthanum chloride also resulted in dose-related increases in ROS and MDA content, as well as decreases in GSH, catalase, SOD, and GSH-Px in the hippocampi. Significantly decreased Nrf2 mRNA and protein expression were observed in the hippocampi in the mid- and high-dose groups. A LOAEL of 115.3 mg La/kg-day based on maternal exposure from drinking water is identified from this study. Critical effects in pups included decreases in body weight, impaired spatial learning and memory (poor performance in Morris water maze), and ultrastructural changes in the hippocampal synapses. A NOAEL could not be identified.

Hu et al. (2018)

In a study that included gestational exposure, pregnant Wistar rats (10/dose) were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.125, 0.25, or 0.5% during lactation (3 weeks). The pups were exposed during lactation and subsequently exposed via drinking water at the same concentrations as their mothers for 1 month postweaning. Water consumption and maternal body weight were not measured. The doses were estimated to be 0, 115.3, 230.6, and 461 mg La/kg-day for dams and 0, 153.7, 307.5, and 615 mg La/kg-day for pups.

At the end of exposure, 6 pups from each dose group (1 pup/litter, 6/10 litters) were examined for lanthanum content in the hippocampus. In addition, 6 pups from each dose group (1 pup/litter, 6/10 litters) were tested in the Morris water maze. After Morris water maze testing, the pups were randomly selected and the hippocampal tissue was collected for the following experiments: TEM examination, extracellular glutamate and glutamine concentration analysis, enzyme activity analysis (Na^+-K^+-ATPase, glutamine synthetase, phosphate-activated

glutaminase), mRNA analyses (glutamate/aspartate transporter [GLAST], glutamate transporter-1[GLT-1], N-methyl-D-aspartate receptor subunit GluN1, GluN2A and GluN2B), protein analyses (glutamine synthetase [GS], phosphate-activated glutaminase [PAG], GLAST, GLT-1, GluN1, GluN2A, and GluN2B) and immunofluorescence analysis (GluN1, GluN2A, and GluN2B). An additional 6 pups from each dose group (1 pup/litter, 6/10 litters) were tested for the electrophysiological analysis and intracellular [Ca^{2+}] analysis. Data analysis consisted of ANOVA for differences among groups followed by SNK test for multiple comparisons.

Lanthanum chloride treatment resulted in statistically significant and dose-dependent increases in lanthanum content in the hippocampus. Statistically significant, dose-related impairments of spatial learning and memory were evident from analysis of Morris water maze performance during the training period (increased escape latency and total distance traveled) and after 5 days resting (increased escape latency and total distance traveled, decreased time spent in target quadrant and number of target quadrant crossings). Of these four metrics, time spent in the target quadrant and number of target quadrant crossings were significantly different from the controls at all doses, while escape latency and total distance traveled were significantly different from controls at the mid and high doses.

Treatment-related alterations in ultrastructure of the CA1 areas of the hippocampus, consisting of indistinct nuclear membranes, changed neuronal karyotheca, invisible cytoplasmic organelles, swollen mitochondria, and nuclear fragmentation (quantitative results not reported). Treatment with lanthanum chloride also resulted in dose-related increases in glutamate and decreases in glutamine concentration in the hippocampi. Significantly decreased GLAST and GLT-1 mRNA expression and protein expression were observed in the hippocampi in all treated dose groups. There were also significant decreases in GS and PAG protein expression and enzyme activity, and Na^{+}-K^{+}-ATPase activity in the hippocampi. The treatment resulted in significant increases in mRNA and protein expression of GluN1, GluN2A, and GluN2B, which was also confirmed by fluorescence intensity analysis and increases in intracellular [Ca^{2+}]. Electrophysiological analysis indicated that after high-frequency stimulation, the population spike amplitude of rats in the treated groups was significantly lower than in the control group. A LOAEL of 115.3 mg La/kg-day based on maternal exposure from drinking water is identified from this study based on impaired spatial learning and memory (poor performance in Morris water maze), and ultrastructural changes in the hippocampal synapses. A NOAEL could not be identified.

Feng et al. (2006a)

Groups of 15 pregnant Wistar rats received lanthanum chloride (purity not reported, vehicle not reported) at daily gavage doses of 0, 0.1, 2, or 40 mg $LaCl_3$/kg-day (0, 0.06, 1, or 23 mg La/kg-day) throughout gestation and lactation (Feng et al., 2006a). At birth, litters were culled to four male and four female pups (when possible). After weaning at PND 20, the offspring were exposed by gavage at the same doses as their mothers, until sacrifice. Pup body weights were recorded at birth and on PNDs 30, 90, and 150. Neurobehavioral developmental landmarks were recorded: pinna detachment was assessed on PND 2, eye opening was assessed on PND 10, surface righting reflex was tested from PNDs 3−5, and swimming endurance was tested on PNDs 12 and 20. Groups of 10 males randomly selected from each exposure level were sacrificed at PND 30 for assessment of deoxyribonucleic acid (DNA) and protein levels in the brain. Among the remaining pups, 12 males and 6 females randomly selected from each group were tested in the Morris water maze at 5 months of age; four trials per day (with 6-minute

rest periods between trials) were performed for 8 days, and mean latency time was recorded for each day. Statistical analyses consisted of ANOVA followed by Student's *t*-test, using the individual pup as the unit of analysis for the postweaning period and one male and one female per litter for the preweaning period.

Litter size, pinna detachment, eye opening, and birth weight were not affected by lanthanum chloride treatment (Feng et al., 2006a). At the highest dose, pup body weights were statistically significantly reduced (11.4 and 8.8% below controls for males and females, respectively) at PND 150; statistically nonsignificant reductions of ≥5% were seen at this dose on PND 90 (see Table B-13). At lower doses and other time points, there were no statistically or biologically significant changes in body weight, apart from an 7.9% increase at 1 mg La/kg-day on PND 90 that did not persist to PND 150. Surface righting reflex times in both sexes were significantly shorter at doses ≥1 mg La/kg-day on PNDs 3 and 4, but not on PND 5; the significance of this finding is uncertain given its lack of persistence. Swimming endurance time was not affected by exposure on PND 12. Swimming endurance on PND 20, while significantly increased at the 1 mg La/kg-day dose, was significantly decreased in both sexes compared to controls at 23 mg La/kg-day, suggesting a toxicological effect at the highest dose. In the Morris water maze testing of offspring at 5 months of age, exposure to the highest dose resulted in significantly increased escape latency on Days 3, 4, and 5 of testing (data shown graphically); no other significant differences were seen. Similar to results seen by Feng et al. (2006b), the control, low-, and mid-dose animals appeared to learn the maze within 3−5 days, reaching a relatively consistent escape latency of ±20 seconds, while high-dose animals learned more slowly, achieving a 20-second latency by the 8th day of testing. Total DNA concentration in the brain was significantly decreased at doses ≥1 mg La/kg-day, but the protein:DNA ratio did not exhibit any treatment-related trends. A LOAEL of 23 mg La/kg-day is identified for this study based on decreased pup body weight, decreased swimming endurance time, and increased escape latency in the Morris water maze; the NOAEL is 1 mg La/kg-day. Changes in swimming endurance time (increased) and surface righting reflex time (shortened) at 1 mg La/kg-day are not judged to be toxicologically significant.

He et al. (2008)

Groups of 10 pregnant Wistar rats were given lanthanum chloride (purity 99.9%, in hydrochloric acid) by daily gavage from GD 0 through parturition and during lactation until PND 20 (He et al., 2008). Doses of 0, 0.1, 2, or 40 mg $LaCl_3$/kg-day were used (0, 0.06, 1, or 23 mg La/kg-day). At birth, litters were culled to 5 males/litter. At weaning, male pups were exposed by gavage at the same doses as their mothers until 6 months of age. Once exposure was concluded, the animals were weighed, and 15 randomly selected rats/group were tested in the Morris water maze; the litter distribution of the selected animals was not reported. Testing consisted of four 2-minute trials per day for 4 consecutive days, in which escape latency, general pathway, and average swimming speed to find a submerged platform were measured. A trial for memory consolidation was performed on the 5th day: the platform was removed and the percentage of time spent in the target quadrant (target quadrant preference) was measured. The final day of testing was to evaluate potential sensorimotor deficits by recording the rats' ability to locate a visible platform. After testing, 7 rats/group were sacrificed for analysis of intracellular free calcium, calcium-ATPase activity, and oxidative stress measures in the hippocampus and cerebral cortex. An additional 4 rats/group from those tested in the water maze were sacrificed for analysis of pyramidal cells in the CA1, CA3, and dentate gyrus (DG) areas of the dorsal hippocampus (neurons were counted manually under light microscopy).

Six rats/group among those not used for water maze testing, were sacrificed for analysis of lanthanum concentration in serum, hippocampus, and cerebral cortex. Comparisons among groups were done using ANOVA and Tukey's tests. Individual rats were the units of statistical analysis.

Body weights of the pups were not affected by exposure to lanthanum chloride (He et al., 2008). All data, except for lanthanum content in the brain, were presented graphically. The data for two measures of performance in the Morris water maze (length of pathway to platform and preference for the target quadrant) and the numbers of pyramidal cells in the CA3 region of the hippocampus were digitized from graphs in the publication using the GrabIt! software and are presented in Table B-14. Lanthanum concentrations in the serum, hippocampus, and cerebral cortex of pups were significantly increased over controls at the highest dose. In water maze testing, a significant impairment of spatial learning and memory was observed. While swimming speed did not differ among the groups, escape latency was significantly increased at the highest dose, and general pathway (total distance) was increased at the mid and high doses. In the test for memory consolidation, preference for the target quadrant was significantly reduced at doses ≥1 mg La/kg-day. In the CA3 region of the hippocampus, significantly lower numbers of pyramidal cells (18−23% lower than controls) were observed at doses ≥1 mg La/kg-day; no changes were observed in other regions of the hippocampus. Intracellular calcium in the hippocampus was significantly increased, while calcium-ATPase activity was decreased, at the highest dose of lanthanum chloride. Oxidative stress markers (increased MDA, decreased catalase, SOD, and/or glutathione peroxidase) in the hippocampus and cerebral cortex were significantly altered by exposure, primarily at the high dose. A LOAEL of 1 mg La/kg-day and a NOAEL of 0.06 mg La/kg-day are identified for these data based on performance in the water maze and decreased numbers of pyramidal cells.

Yang et al. (2009)

Yang et al. (2009) conducted a lactational and drinking water exposure study of lanthanum chloride in Wistar rat pups. Lactating Wistar rats were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.25, 0.5, or 1% for 3 weeks, exposing their pups (~4/sex/litter and 8 litters/dose) from birth to PND 21 by lactation. Pups were then exposed directly via drinking water for 1 month at the same concentrations as the dams. Water consumption and maternal body weight were not measured. The doses were estimated as described previously for Zheng et al. (2013) to be approximately 0, 230.6, 461, and 923 mg La/kg-day for dams and 0, 307.5, 615, and 1,230 mg La/kg-day for pups. At the end of exposure, the pups were trained in the Morris water maze for 5 days, rested for a week, and then retested. Escape latency time was measured. After testing, the animals were sacrificed; lanthanum content of the hippocampus was measured, and the hippocampal synaptic structure (area CA1 only) was examined by TEM. Expressions of pCaMK IV, pMAPK, pPKA, pCREB, c-fos, and egr1 proteins in the hippocampus were evaluated by Western blotting and densitometric analysis. Statistical comparisons among groups employed an ANOVA followed by a SNK test. The litter was the unit of statistical analysis.

The lanthanum content of the hippocampus increased with dose to a maximum of ~0.055 µg/g tissue (compared with <0.005 in controls) (Yang et al., 2009). Dose-related impairments of spatial learning and memory were evident from Morris water maze performance. During training Days 2, 3, and 4, significant, dose-related increases in escape latencies were

observed at all doses, indicating that the exposed rats had difficulty learning the maze. No differences were seen on training Day 5 (see Table B-15). During retesting on Day 12 (after the rest week), the exposed rats exhibited significantly longer escape latencies compared with their Day 5 results and with controls, indicating impaired recall of the maze. The synaptic ultrastructure of CA1 area in the hippocampus was significantly altered by exposure to lanthanum chloride; changes in the exposed animals included fewer synaptic vesicles, short active synaptic zone, uneven synaptic curvature, and thin postsynaptic density (quantitative data not provided). Hippocampal expressions of pCaMK IV, pMAPK, pCREB, c-fos, and egr1 proteins were significantly reduced by treatment in a dose-dependent fashion. These data indicate a LOAEL of 230.6 mg La/kg-day based on maternal exposure from drinking water (the lowest dose tested) based on impaired spatial learning and memory (as tested in Morris water maze), and ultrastructural changes in the hippocampal synapses of area CA1. A NOAEL could not be identified.

Yang et al. (2013)

A subsequent study by the same laboratory used an identical exposure regimen [see Yang et al. (2009)]. Water consumption and maternal body weight were not measured. The doses were estimated as described previously for Zheng et al. (2013) to be approximately 0, 230.6, 461, and 923 mg La/kg-day for dams, and 0, 307.5, 615, and 1,230 mg La/kg-day for pups. At the end of exposure, the pups were sacrificed, and the hippocampi were removed for evaluation of Nissl body levels (measured as integrated optical density in CA1, CA3, and DG areas), neuronal ultrastructure (by TEM, CA1 area only), apoptosis, glutamate level, intracellular calcium level, and endoplasmic reticulum (ER) stress markers. Statistical analyses employed an ANOVA followed by a SNK test (for differences among groups). The litter was the unit of statistical analysis.

All results were presented graphically in this study. A dose-related increase in the concentration of lanthanum ion in the hippocampus (from ~0.02 to ~0.06 µg/g tissue) was observed in the treated rats (Yang et al., 2013). Treatment with lanthanum chloride resulted in dose-related decreases in the levels of Nissl bodies (indicative of neural degeneration) in the CA1 and DG areas of the hippocampus that were significantly different from control at all doses, and a decrease in Nissl body levels in the CA3 area that was significant at doses ≥461 mg La/kg-day. In addition, alterations in the neuronal ultrastructure (chromatin condensation and nuclear fragmentation) of the CA1 area of hippocampus were observed in treated rats, but not in control rats (quantitative data not reported). Dose-related, statistically significant increases in apoptosis, glutamate levels, and intracellular calcium levels were measured in the hippocampi at all doses. The lowest dose in this study is identified as a LOAEL of 230.6 mg La/kg-day based on maternal exposure from drinking water based on reduced levels of Nissl bodies and ultrastructural changes in the hippocampal neurons. A NOAEL could not be identified.

Liu et al. (2014)

A third study by this laboratory (Liu et al., 2014) extended the exposure duration by 1 month. Lactating Wistar rats were given drinking water containing lanthanum chloride (purity 99.9%) at concentrations of 0, 0.25, 0.5, or 1% for 3 weeks, exposing their pups (number reported only as eight/group) from birth to PND 21 by lactation. The pups were subsequently exposed via drinking water at the same concentrations as their mothers for 2 months. Water consumption was not measured. The doses were estimated to be 0, 230.6, 461, and

923 mg La/kg-day for dams and 0, 307.5, 615, and 1,230 mg La/kg-day for pups. At the end of exposure, the pups were tested for learning and memory in the Morris water maze. The rats were first trained for 5 consecutive days to find a platform in the pool, and then rested for a week before testing, during which escape latency, path length, and navigation path were measured. One hour later, the platform was removed and the rats were allowed to swim for 60 seconds, during which the number of target quadrant crossings, time spent and distance travelled in the target quadrant, time from first entry to the target quadrant, and track plots were recorded. Following testing, the pups were sacrificed, and the lanthanum contents of the hippocampi were analyzed. Examination of the hippocampal synapses by TEM was performed. In addition, analysis of the hippocampi for protein and mRNA levels of several genes involved in the ERK/MSK1 signaling pathway was conducted. The data were analyzed using an ANOVA with a post hoc SNK test. The litter was the unit of statistical analysis for the water maze performance metrics; for hippocampal synaptic metrics, individual synapses were the unit of analysis (50/group, litter distribution not reported).

All data were presented graphically. The concentration of lanthanum in the hippocampus was increased with exposure from ~0.025 µg/g tissue at the low dose to ~0.052 µg/g tissue at the high dose, demonstrating that lanthanum was absorbed from the drinking water and crossed the blood-brain barrier (Liu et al., 2014). Testing in the Morris water maze showed that exposure to lanthanum chloride resulted in dose-related impairments of spatial learning and memory. During the 5-day training period, dose-related increases in escape latency were observed on Days 3 and 4 (statistically significantly different from control at all doses on Day 3, and at the two higher doses on Day 4). In addition, distance traveled was significantly longer at the high dose on Day 3 and at the mid and high doses on Day 4. By Day 5, all groups performed similarly. Dose-related increases in both escape latency (significant at all doses) and distance traveled (significant at the mid and high doses) were also observed in the place navigation test after the 1-week rest period. Testing for spatial memory (with platform removed) showed dose-related reductions (significant at all doses) in number of target quadrant crossings, time spent in the target quadrant, and distance travelled in the target quadrant, as well as a significant, dose-related increase in latency to first entry into the target quadrant. TEM examination of the hippocampus showed dose-related effects on the synaptic interface structure that consisted of decreases in the thickness of the postsynaptic density, length of the active zone, and synaptic curvature. These changes were statistically significantly different from control at all doses (see Table B-16). Lanthanum chloride exposure decreased the expression of several genes involved in the ERK/MSK1 signaling pathway, including p-MEK1/2, p-ERK1/2, p-MSK1, p-CREB, c-FOS, and BDNF. In this study, the lowest dose was associated with impairments in Morris water maze performance (both learning and memory), as well as alterations in the morphology of the hippocampal synapses; therefore, the low dose is a LOAEL of 230.6 mg La/kg-day based on maternal exposure from drinking water (the lowest dose tested).

Inhalation Exposures

No studies of animals exposed to lanthanum or its soluble salts via inhalation have been identified in the available literature.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A provides an overview of genotoxicity studies, and Table 4B provides an overview of other supporting studies on lanthanum and soluble salts, including 1 acute oral

lethality study, 1 short-term-duration (5 days) oral toxicity study, and 24 toxicity studies using exposure routes other than oral or inhalation.

Table 4A. Summary of Genotoxicity of Soluble Lanthanum

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies in prokaryotic organisms						
Mutagenicity	*Salmonella typhimurium* strains TA97, TA98, TA100, TA1535	0, 3.3, 10, 33, 100, 333, 1,000, 3,333, 10,000 µg/plate $LaCl_3$	−	−	Precipitate was present at ≥10 µg/plate. Cytotoxicity was observed in TA97 at 10,000 µg/plate without S9 and ≥3,333 µg/plate with S9. A slight clearing of background lawn was noted at ≥3,333 µg/plate in TA98.	Zeiger et al. (1992)
DNA adducts	*Escherichia coli* Q13	0, 100, 1,000 µM $La(CH_3COO)_3$	+	+	Measured by ^{32}P-postlabeling. $La(CH_3COO)_3$ induced DNA adducts in the presence and absence of S9 activation or lysozyme or both.	Kubinski et al. (1981)
DNA repair	*Bacillus subtilis* strains H17 (Rec+, *arg-, trp-*) and M45 (Rec-, *arg-, trp-*)	0.00−0.5 M $LaCl_3$ and $La(NO_3)_3$	−	NT	Using rec assay with cold incubation. Plates were held at 4°C for 24 hr, then incubated overnight at 37°C. $La(NO_3)_3$ and $LaCl_3$ were highly toxic, but did not induce DNA damage.	Kanematsu et al. (1980)
DNA repair	*B. subtilis* strains H17 (Rec+, *arg-, trp-*) and M45 (Rec-, *arg-, trp-*)	0.05 M $LaCl_3$	−	NT	Using rec assay.	Nishioka (1975)
Genotoxicity studies in mammalian cells—in vitro						
MN	Human peripheral lymphocytes incubated with $La(NO_3)_3{\cdot}nH_2O$ for 48 hr	0, 0.016, 0.04, 0.1, 0.25, 0.625 mM La	+	NT	$La(NO_3)_3{\cdot}nH_2O$ induced dose-related increase in MN frequency at concentrations ≥0.25 mM La. Cytotoxicity was observed, with LC_{50} of 0.108 mM La in this system.	Yongxing et al. (2000)
DNA strand breaks	Human peripheral lymphocytes incubated with $La(NO_3)_3{\cdot}nH_2O$ for 1.5 hr	0, 0.004, 0.008, 0.016, 0.03 mM La	+	NT	Single cell gel electrophoresis (comet) assay. $La(NO_3)_3{\cdot}nH_2O$ induced dose-related increase in single strand DNA breaks at concentrations of 0.04 mM La. Cytotoxicity was observed, with LC_{50} of 0.108 mM La in this system.	Yongxing et al. (2000)
Unscheduled DNA synthesis	Human peripheral lymphocytes incubated with $La(NO_3)_3{\cdot}nH_2O$ for 4.5 hr	0, 0.004, 0.008, 0.016, 0.03 mM La	+	NT	3H-TdR incorporation assay. $La(NO_3)_3{\cdot}nH_2O$ induced dose-related increase in unscheduled DNA synthesis at concentrations of 0.04 mM La. Cytotoxicity was observed, with LC_{50} of 0.108 mM La in this system.	Yongxing et al. (2000)

Table 4A. Summary of Genotoxicity of Soluble Lanthanum

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	References
Genotoxicity studies—in vivo						
Bone marrow mitotic index	Albino rats (number/sex/group not specified); $LaCl_3$ was administered i.p. every 24 hr for up to 4 d (sacrificed at 24, 48, 72, or 96 hr), or as a one-time dose with sacrifice 72, 96, or 110 hr later	Dose reported only as one-fourth the LD_{50}	−	NA	$LaCL_3$ caused a decrease in the mitotic frequency with repeated dosing; however, after a ≥72-hr recovery, frequency was comparable to controls.	De and Sharma (1981)
CAs	Albino rats (number/sex/group not specified); $LaCl_3$ was administered i.p. every 24 hr for up to 4 d (with sacrifice at 24, 48, 72, or 96 hr), or as a one-time dose with sacrifice 72, 96, or 110 hr later	Dose reported only as one-fourth the LD_{50}	±	NA	Total CAs were significantly increased 24 hr after the initial dose, but did not increase substantially with successive doses. After a 72-hr recovery, numbers of aberrations were comparable to controls.	De and Sharma (1981)

[a]+ = positive; ± = weakly positive; − = negative; NA = not applicable; NT = not tested.

CA = chromosomal aberration; DNA = deoxyribonucleic acid; i.p. = intraperitoneal; La = lanthanum; $La(CH_3COO)_3$ = lanthanum acetate; $LaCl_3$ = lanthanum(III) chloride; $La(NO_3)_3$ = lanthanum(III) nitrate; $La(NO_3)_3 \cdot nH_2O$ = lanthanum nitrate hydrate; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; MN = micronuclei.

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Acute/short-term oral exposure				
Acute oral lethality	Aqueous solutions of lanthanum chloride, lanthanum nitrate, or lanthanum ammonium nitrate were administered orally to S-D rats (sex not specified) for determination of LD_{50} values. The rats were observed for at least 10 d.	Details of time to death and clinical signs were not reported. The study author reported that there were no sex differences in lethality.	Oral LD_{50} values: $LaCl_3$ = 2,370 mg La/kg-d; $La(NO_3)_3$ = 1,450 mg La/kg-d; $La(NO_3)_4NH_4$ = 830 mg La/kg-d	Dubois (1956); Cochran et al. (1950)
Short-term oral toxicity	$LaCl_3$ was administered to groups of 3 male Wistar rats in drinking water at a dose estimated by the study authors to be 0.77−0.9 mmol $LaCl_3$/kg-d (up to ~125 mg La/kg-d) for 5 d. At sacrifice at the end of exposure, the ileum, liver, spleen, kidney, lung, heart, brain, leg muscle, and tongue muscle were weighed and examined microscopically.	There were no effects of treatment on organ weights or histopathology.	$LaCl_3$ at an oral dose of 125 mg La/kg-d for 5 d did not affect major organs of the rat.	Rabinowitz et al. (1988)
Other route single exposure				
Acute i.p. lethality	$La(NO_3)_3$ was administered i.p. to 35 female CF1 mice; the animals were observed for 30 d.	For all the lanthanides tested, most mice died within the first 8 d after dosing. 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 La were not reported.	Female mouse i.p. LD_{50} = 131 mg La/kg	Bruce et al. (1963)
Acute i.p. lethality	$LaCl_3$ was administered i.p. to CFW albino mice (sex and number not specified) at doses of 170 or 283 mg La/kg; the animals were observed for 7 d.	33 and 77% of mice died at 170 and 283 mg La/kg, respectively. Mean times to death were 32 and 37 hr, respectively.	Mouse i.p. LD_{50} = 205 mg La/kg	Graca et al. (1962)
Acute i.p. lethality	$LaCl_3$ was administered i.p. to guinea pigs (strain, sex, and number not specified) at doses of 28, 57, or 85 mg La/kg; the animals were observed for 7 d.	5, 22, and 61% of guinea pigs died at 28, 57, and 85 mg La/kg, respectively. Mean times to death were 154, 54, and 45 hr, respectively.	Guinea pig i.p. LD_{50} = 76 mg La/kg	Graca et al. (1962)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Acute i.p. lethality	Aqueous solutions of $LaCl_3$, $La(NO_3)_3$, or $La(NO_3)_4NH_4$ were administered i.p. to S-D rats (sex not specified) for determination of LD_{50}. The rats were observed for at least 10 d.	Details of time to death and clinical signs were not reported. The study author reported no sex differences in lethality.	Rat i.p. LD_{50} values: $LaCl_3$ = 197 mg La/kg-d; $La(NO_3)_3$ = 145 mg La/kg-d; $La(NO_3)_4NH_4$ = 153 mg La/kg-d	Dubois (1956)
Acute i.v. toxicity	Male and female dogs (breed and sex not specified, 3/group) received i.v. injections of chlorides of 15 lanthanide elements. Ten doses of 10 mg $LaCl_3$/kg (6 mg La/kg) each were injected at 10-min intervals. Blood samples were collected before treatment and 0, 10, 30, 60, 100, and 160 min after treatment for analysis of erythrocyte, leukocyte, and differential cell counts, prothrombin and coagulation time, hemoglobin, sedimentation, and Hct. After 160 min, 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. Some animals died from treatment (14/45 treated with chlorides), but the mortality was not reported by element. $LaCl_3$ treatment resulted in a steady decline in blood pressure (down to about 60% of pretreatment values) and heart rate (to about 70% of pretreatment values) over the 160-min observation period. Respiratory rates were increased between 60−160 min postdosing. $LaCl_3$ resulted in increases in (to >100 sec by 60 min after treatment) and coagulation time (to >60 min by 30 min after treatment). Visual observation of pooled blood at incision sites provided additional evidence of the effect of lanthanide elements on clotting parameters, but the incidence or specific treatment group(s) where this was observed were not reported. Gross and histopathological examinations revealed slight to moderate hyperemia of the lungs.	i.v. exposure to $LaCl_3$ impaired clotting in dogs.	Graca et al. (1964)
Acute i.v. toxicity	Mixed breed rabbits (strain, sex, and *n*/group not specified) received single i.v. doses of 0 or 20−100 mg $LaCl_3$/kg (10−60 mg La/kg) or 2−5 repeated doses of 10 mg $LaCl_3$/kg (6 mg La/kg). Hemostasis parameters (prothrombin activity, prothrombin consumption, PTT, thrombin time, fibrinogen, thromboelastogram, thrombocyte count, thrombocyte factor 3, and ADT-induced thrombocyte aggregation) were evaluated (timing of evaluation not reported).	Results were not reported by dose. A single large dose of $LaCl_3$ (20−100 mg $LaCl_3$/kg) induced severe, acute hemorrhagic diathesis in some animals, as well as decreased PT and increased PTT. Repeated small doses (2−3 doses of 10 mg $LaCl_3$/kg each) decreased prothrombin consumption and increased fibrinogen without affecting other parameters.	i.v. exposure to $LaCl_3$ impaired clotting in rabbits.	Nagy et al. (1976)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Acute i.v. toxicity	Male ddY mice (3−6/group) were treated with a single i.v. dose of 20 or 200 µmol La/kg (3 or 30 mg La/kg) as $LaCl_3$. 5 d after dosing, the animals were sacrificed for assessment of testes weight and histology, as well as lipid peroxidation and calcium content in the testes.	Body weights were significantly lower than controls at 200 µmol La/kg but not at the low dose. Testes weight, histology, and lipid peroxidation level were not affected by exposure. The testicular calcium concentration was significantly increased at both doses of $LaCl_3$.	i.v. exposure to $LaCl_3$ increased testicular calcium concentration in mice.	Nagano et al. (2000)
Acute intratracheal instillation toxicity	Male Wistar rats (4/group) received a single intratracheal instillation of $LaCl_3$ at doses of 0, 0.5, 1, 10, 20, 50, 100, or 200 µg La/rat and were sacrificed 2 d later. Lanthanum, calcium, phosphorus, and sulfur were measured in the lung, BALF, femur, pulmonary hilum lymph node, plasma, liver, and kidney. BALF samples were analyzed. A separate group of 4 rats was exposed to 50 µg La/rat and sacrificed 1, 2, 3, or 14 d later for light microscopy, TEM, and X-ray microanalysis of the lung.	Histopathology of the lung showed increased numbers of eosinophils. Alveolar macrophages of exposed rats (50 µg La/rat) exhibited many electron-dense granular inclusions; electron-dense layers were seen on the surface and in the basement membrane of Type 1 pneumocytes. Analysis of BALF 2 d after exposure showed dose-related changes in LDH, *β*-glucuronidase, protein, and sulfur, calcium, and phosphorus content, as well as dose-related increases in macrophage, PMN, and eosinophil counts. The half-life for La in the lung was 244 d.	Intratracheal exposure to 50 µg La/rat induced histopathology changes in the lungs and evidence for toxicity in BALF.	Suzuki et al. (1992)
Other route short-term toxicity				
Short-term i.p. toxicity in mice	Male CD-1(ICR) mice (15/group) received daily i.p. injections of $LaCl_3$ (0 or 20 mg $LaCl_3$/kg, equivalent to 0 or 11 mg La/kg-d) for 14 d. Animals were examined daily for mortality and symptoms. At sacrifice at the end of exposure, the mice were weighed, and brains were weighed and examined microscopically. Measures of oxidative stress in the brain were analyzed.	Exposure did not affect survival, body-weight gain, relative brain weight, or brain histology. No significant effect was seen on O_2- or H_2O_2-generating rates, MDA content, or activities of SOD, catalase, ascorbate peroxidase, or glutathione peroxidase in the brain. Significant decreases in the ratios of AsA:DAsA and GSH:GSSG, and in the total antioxidant capacity of the brain were observed with $LaCl_3$ treatment. In addition, iNOS activity was significantly decreased by exposure. Glutamate content and AChE activity were significantly increased by exposure to $LaCl_3$.	i.p. exposure to 11 mg La/kg for 14 d did not affect brain weight or histology in mice.	Zhao et al. (2011)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term i.p. toxicity in mice	Male CD-1(ICR) mice (10/group) received daily i.p. injections of $LaCl_3$ (0 or 20 mg $LaCl_3$/kg, equivalent to 0 or 11 mg La/kg-d) for 14 d. Animals were examined daily for mortality and symptoms. Blood was collected for analysis of serum chemistry. At sacrifice at the end of exposure, the mice were weighed, and livers were weighed and examined microscopically. Expression levels of inflammatory cytokines in the serum and liver were also measured.	Exposure did not affect survival, body-weight gain, or relative liver weight. Serum ALT, pseudocholinesterase, and total bilirubin were significantly increased by exposure, while the ratio of albumin:globulin, triglycerides, total cholesterol, and both HDL- and LDL- cholesterol were decreased. Mild histopathology changes in the liver consisted of basophilia in a few hepatocytes and congestion of the central vein. Significant increases in the expression of inflammatory cytokines (NF-κB, MIF, IL-6, IL-1β, CRP, TNF-α, IL-4, and IL-10) were observed in the serum and liver.	i.p. exposure to 11 mg La/kg for 14 d induced mild liver lesions and serum chemistry changes in mice.	Fei et al. (2011)
Short-term i.v. toxicity in rats	White rats of both sexes (strain and numbers not reported) received i.v. injection of 1.2 mg $LaCl_3$/kg-d (0.7 mg La/kg-d) for 2 or 4 d. At sacrifice, the liver was examined microscopically and analyzed for enzyme activity (nonspecific esterase, acid phosphatase, phosphorylase, LDH, MDH, and SDH).	No details of general animal health were reported. Exposure to $LaCl_3$ for 2 or 4 d resulted in decreases in esterase, phosphorylase, SDH, LDH, and MDH activities; statistical analysis of the changes was not reported. Histopathological changes in the livers of exposed animals were described as "diffuse cellular lesions" after 2 d of exposure and "specific necrobiosis" after 4 d.	i.v. injection of 0.7 mg La/kg-d for 2 or 4 d resulted in liver lesions in rats.	Kádas et al. (1973)
Short-term i.v. toxicity in rats	Groups of 4 white rats of both sexes (strain not reported) received i.v. injection of 1.2 mg $LaCl_3$/animal-d (0.7 mg La/animal-d) for 2 or 4 d, or a single dose of 15 mg $LaCl_3$/animal (8 mg La/animal). At sacrifice 1 or 24 hr after dosing, the liver was examined by light and electron microscopy.	No details of general animal health were reported. Light microscopy revealed changes corresponding to those described in Kádas et al. (1973). Ultrastructurally, the "diffuse cellular lesions" consisted of enlarged nucleoli, irregularly shaped aggregates of glycogen granules or scarce glycogen granules, and focal areas of vesicular transformation of rough ER. Electron-dense granules were seen in the bile canaliculi. The "specific necrobiosis" changes were seen on electron microscopy as swollen centrilobular cells, decreased rough ER and increased vesicular-type ER, increased numbers of mitochondria with decreased electron density and partially destroyed cristae, and swollen biliary epithelium.	i.v. injection of 0.7 mg La/kg-d for 2 or 4 d resulted in liver lesions in rats.	Kádas et al. (1974)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Short-term i.v. toxicity in rabbits	Male rabbits (strain not reported, total $n = 28$) received single or repeated i.v. injections of 29−310 mg $LaCl_3$ (16−176 mg La) for 1−28 d. A control group of 2 rabbits was untreated. At sacrifice, the liver, spleen, kidney, heart, lungs, GI tract, pancreas, bone marrow, adrenal gland, and testes were examined for gross and microscopic pathology.	Gross findings included hyperemia in the lungs and pale livers in exposed animals. Among rabbits exposed for acute durations (up to 1 d), the primary microscopic finding was characterized as "diffuse cellular lesions" in the liver. With prolonged exposure or higher doses, histopathology findings included the diffuse lesions as well as "specific necrobiosis."	i.v. injection of $LaCl_3$ resulted in lung hyperemia and hepatic lesions.	Kádas and Jobst (1973)
Short-term intranasal instillation toxicity in mice	Male CD-1(ICR) mice (15/group) received daily intranasal instillations of $LaCl_3$ (0 or 20 mg $LaCl_3$/kg, equivalent to 0 or 11 mg La/kg-d) for 14 d. Animals were examined daily for mortality and symptoms. At sacrifice at the end of exposure, the mice were weighed, and lungs were weighed. Measures of oxidative stress in the lung were analyzed.	Exposure did not affect survival, body-weight gain, or relative lung weight. No effect on O_2, H_2O_2, or NO production rates was seen. A significant increase in lung MDA content was observed, and SOD, total antioxidant capacity, and ratio of GSH:GSSG in the lung were significantly decreased.	Intranasal instillation of 11 mg La/kg-d increased oxidative stress measures in the lung in mice without affecting lung weight.	Li et al. (2010)
Other route chronic toxicity				
Chronic i.v. toxicity in rats	Male rats (strain not reported, total $n = 103$) received single or repeated i.v. injections of 0.6−30 mg $LaCl_3$ (0.3−17 mg La) for 1−95 d. A control group of 5 rats was untreated. At sacrifice, the liver, spleen, kidney, heart, lungs, GI tract, pancreas, bone marrow, adrenal gland, and testes were examined for gross and microscopic pathology.	Gross findings included hyperemia in the lungs and livers of exposed animals. Among rats exposed for acute durations (up to 1 d), the primary microscopic finding was characterized as "diffuse cellular lesions" in the liver. With prolonged exposure or higher doses, histopathology findings included the diffuse lesions as well as "specific necrobiosis."	Chronic i.v. exposure to $LaCl_3$ resulted in lung hyperemia and hepatic lesions.	Kádas and Jobst (1973)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Chronic intranasal instillation toxicity in mice	Male CD-1(ICR) mice (30/group) received nasal instillation of $LaCl_3$ daily for 6 mo at doses of 0, 2, 5, or 10 mg $LaCl_3$/kg-d (0, 1, 3, or 6 mg La/kg-d). Toxicological evaluations included mortality, signs of toxicity, body weight, BALF analysis, and lung weight and histology. Oxidative stress markers in the lung were measured.	A dose-related decline in body-weight gain was observed, with statistically significant changes at all doses. Lung weight relative to body weight was increased at ≥3 mg La/kg-d. Significant increases in macrophages, lymphocytes, neutrophils, eosinophils, LDH, ALP, and total protein were observed in BALF at all exposure levels. Lung histopathology changes in exposed mice included abscission or fragmentation of epithelial cells, edema, infiltration of inflammatory cells, and thickening of pulmonary interstitium at all exposures. Oxidative stress markers were significantly increased at all exposures.	Intranasal instillation of $LaCl_3$ at 1 mg La/kg-d for 6 mo resulted in decreased body weight and lung lesions.	Hong et al. (2015)
Other route developmental toxicity				
Developmental toxicity after i.p. exposure of mice	Pregnant ICR Swiss albino mice (11−28) received a single i.p. injection of 44 mg La/kg on GDs 4, 6, 8, 10, 12, 14, or 16. Controls received deionized water on GDs 14 or 16. Fraction of females continuing pregnancy and average litter size were recorded. In a separate experiment, groups of 16 pregnant mice were exposed on GD 4 and implantation sites were recorded at sacrifice on GD 5.	The fraction of females continuing pregnancy was significantly decreased from control in groups exposed to $LaCl_3$ on GDs 4, 6, 14, and 16. In addition, average litter size per continuing pregnancy was significantly decreased in groups exposed on GDs 4, 12, 14, and 16. Exposure on GD 4 significantly decreased the numbers of females with at least one implantation site and the average number of implantation sites per pregnant female on GD 5.	i.p. exposure of mice to $LaCl_3$ impaired pregnancy maintenance, decreased litter size, and decreased implantations.	Abramczuk (1985)
Other route neurotoxicity				
Neurotoxicity after i.p. exposure of rats	Male albino Wistar rats (7/group) received daily i.p. injections of $LaCl_3 \cdot 7H_2O$ (53 mg $LaCl_3 \cdot 7H_2O$/kg or 20 mg La/kg) for 7 consecutive d. One hr after the last dose, the rats were sacrificed. Total antioxidant status and activities of AChE, Na^+/K^+-ATPase, and Mg^{2+}-ATPase activities in the brain were determined.	The study authors reported that there were no behavioral or physiological effects of treatment (no details of evaluations provided). Exposure resulted in a significant decrease (36% relative to controls) in brain total antioxidant status. Na^+/K^+-ATPase activity was significantly decreased (28%), as was Mg^{2+}-ATPase activity (8%). A significant increase in AChE activity in the brain (23%) occurred in treated rats. Cotreatment with cysteine partially mitigated the effects on total antioxidant status and AChE activity but not the effects on ATPase activity.	i.p. exposure of rats to $LaCl_3 \cdot 7H_2O$ increased AChE activity in the brain and decreased total antioxidant status in the brain.	Liapi et al. (2009)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Neurotoxicity after s.c. exposure of rats	Pregnant Long-Evans rats received a single dose of 175 mg $LaCl_3$/kg (100 mg La/kg) by s.c. injection on GD 10 and dams were allowed to deliver. Pups were weighed daily from PNDs 4−14. Between PNDs 18−22, the pups were tested every other day for swimming behavior. Swim ability was scored between 0 (unable to get nose out of water) to 3 (able to get nose and more than half of head out of water).	Pup weights were not affected by exposure. Swimming scores were lower than controls in exposed rats on PNDs 8, 10, 14, and 18, but by PND 22, all pups were scored similarly.	s.c. exposure to $LaCl_3$ in utero temporarily delayed swimming behavior in rats.	Wadkins et al. (1998)
Neurotoxicity after intracerebro-ventricular injection in rats	Male Wistar rats (5/group) received lanthanum (0, 0.1, 1.0, or 10.0 mM $LaCl_3$ or 0, 0.06, 0.6, or 6 mM La) by intracerebroventricular injection, followed by i.p. injection of cocaine (0 or 10 mg/kg). Motor activity was recorded at 15-min intervals after exposure.	Exposure to lanthanum did not affect motor activity in rats not exposed to cocaine. In rats exposed to cocaine, La treatment at concentrations ≥0.6 mM prevented the increase in motor activity induced by cocaine.	Intracerebroventricular exposure to $LaCl_3$ inhibited cocaine-induced motor activity in rats.	Kuzmin and Zwartau (1996)
Neurotoxicity after intracranial injection in rats	S-D rats (number and sex not specified) received microinjections of $LaCl_3$ (83 or 47 µg La) in the brain. Antinociceptive response was measured by tail flick and hot plate tests at intervals between 15−120 min after exposure.	Exposure to $LaCl_3$ inhibited responses in the tail flick and hot plate tests 30 and 60 min after exposure, but not 120 min after exposure. Coexposure to $CaCO_3$ blocked the effect of $LaCl_3$.	Intracranial exposure to $LaCl_3$ induced an analgesic effect in rats.	Harris et al. (1975)
Neurotoxicity after intracranial injection in chicks	Lohmann brown domestic chicks (8/group) received a single intracranial injection of lanthanum chloride (0, 1, 5, or 10 mM, or 0, 0.6, 3, or 6 mM La) 1 wk after hatching. The chicks were weighed every 2 d for 7 d. The chicks were observed for locomotor activity 2 d after exposure, and tested for detour learning (ability of animal to reach goal when an obstacle is placed between subject and goal; considered a functional test for CNS development) daily from 3−7 d postexposure.	$LaCl_3$ exposure did not affect body weight or horizontal locomotion. Significant delays in response latency were seen in the tests of detour learning among chicks exposed to ≥3 mM La.	Intracranial injection of $LaCl_3$ impaired detour learning in chicks.	Che et al. (2011)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	References
Neurotoxicity in chicks after injection in embryonic eggs	Fertilized chick eggs (46/group) were injected with lanthanum chloride (0, 0.1, 2, or 40 mg $LaCl_3$/kg, or 0, 0.06, 1, or 20 mg La/kg) on embryonic D 9−16. 1 d after hatching, the chicks were tested in a one-trial passive avoidance learning task (avoidance of pecking a bead with a bad flavor) as a measure of long-term memory. After sacrifice at the end of testing, La content in the intermediate medial mesopallium and medial striatum portions of the brain was measured.	There were no effects on egg weight, hatch day, or hatch weight; however, hatch rate declined with dose from 85% for saline-injected eggs to only 6.5% for eggs exposed to 20 mg La/kg. Because the number of chicks was so low in the group exposed to 20 mg La/kg, neurobehavioral testing was not conducted in this group. Significantly decreased mean avoidance rate was observed in chicks after exposure to 1 mg La/kg, but not at the low dose. Significantly increased La concentrations in the brain were noted at both 0.06 and 1 mg La/kg.	Injection of $LaCl_3$ into chick eggs resulted in impaired long-term memory in chicks.	Che et al. (2009)
Neurotoxicity after intracranial injection in chickens	Day-old black Australorp × white Leghorn chickens (16/group) received intracranial injection of $LaCl_3 \cdot 7H_2O$ (5 mM or 2 mM La) immediately after a visual reminder for the passive learning avoidance test they had previously mastered. The chicks were retested at various time points after the reminder.	Exposure resulted in transient loss of memory on retesting, only when the test material was administered after a visual reminder. The deficit remained when testing occurred up to 40 min after the reminder; in later testing (60 and 180 min after the reminder), there was no difference from control.	Intracranial exposure to $LaCl_3$ inhibited immediate memory recall in chicks.	Summers et al. (1996)

AChE = acetylcholinesterase; ADT = androgen deprivation therapy; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AsA = L-ascorbate; BALF = bronchoalveolar lavage fluid; $CaCO_3$ = calcium carbonate; CNS = central nervous system; DAsA = dehydroascorbate; ER = endoplasmic reticulum; GD = gestation day; GI = gastrointestinal; GSH = glutathione; GSSG = oxidized glutathione; H_2O_2 = hydrogen peroxide; Hct = hematocrit; HDL = high-density lipoprotein; iNOS = inducible nitric oxide synthase; i.p. = intraperitoneal; i.v. = intravenous; K = potassium; La = lanthanum; $LaCl_3$ = lanthanum(III) chloride; $LaCl_3 \cdot 7H_2O$ = lanthanum(III) chloride heptahydrate; $La(NO_3)_3$ = lanthanum(III) nitrate; $La(NO_3)_4NH_4$ = lanthanum ammonium nitrate; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MDA = malondialdehyde; MDH = malate dehydrogenase; Mg = magnesium; Na = sodium; NO = nitrogen oxide; O_2 = oxygen; PMN = polymorphonuclear leukocyte; PND = postnatal day; PT = prothrombin time; PTT = partial thromboplastin time; s.c. = subcutaneous; S-D = Sprague-Dawley; SDH = succinic dehydrogenase; SOD = superoxide dismutase; TEM = transmission electron microscopy.

Genotoxicity

Lanthanum chloride yielded negative results when tested in vitro for mutagenicity in *Salmonella* (Zeiger et al., 1992) and for DNA repair in *Bacillus subtilis* using the rec assay (Kanematsu et al., 1980; Nishioka, 1975). In an in vivo rat test, intraperitoneal (i.p.) administration of lanthanum chloride at a dose reported only as one-fourth the median lethal dose (LD_{50}) did not increase the bone marrow mitotic frequency, but did induce a transient increase in the chromosome aberration (CA) (De and Sharma, 1981). A single study (Kubinski et al., 1981) in *Escherichia coli* showed increased DNA adduct formation with exposure to lanthanum acetate; no other studies of this compound were located. Lanthanum nitrate induced increased frequencies of MN and DNA strand breaks, and unscheduled DNA synthesis in human peripheral lymphocytes tested in vitro without metabolic activation (Yongxing et al., 2000), but did not increase DNA repair in *B. subtilis* in a rec assay with cold incubation (Kanematsu et al., 1980). In summary, the mutagenicity and genotoxicity data for soluble lanthanum salts are limited, but available data suggest that lanthanum nitrate may be genotoxic in human lymphocytes.

Acute and Short-Term-Duration Oral Studies

Oral LD_{50} values of 2,370, 1,450, and 830 mg La/kg were reported for lanthanum chloride, lanthanum nitrate, and lanthanum ammonium nitrate, respectively, in S-D rats (Dubois, 1956; Cochran et al., 1950). A 5-day exposure of male Wistar rats to 125 mg La/kg-day in drinking water did not result in effects on organ weights or histopathology changes in major organs (Rabinowitz et al., 1988).

Other Route Toxicity Studies

Intraperitoneal lethality studies suggest low oral absorption of soluble lanthanum compounds; i.p. rat LD_{50} estimates were between one-fifth and one-twelfth of corresponding oral values (197, 145, and 153 mg La/kg for lanthanum chloride, lanthanum nitrate, and lanthanum ammonium nitrate, respectively, when administered i.p., compared with 2,370, 1,450, and 830 mg La/kg when administered orally) (Dubois, 1956). Lethality data, while limited, provide some evidence for species differences in susceptibility to i.p.-administered $LaCl_3$; the guinea pig LD_{50} was 76 mg La/kg, compared with 205 mg La/kg for mice in the same study (Graca et al., 1962). This also is supported by mice LD_{50} reported by Bruce et al. (1963).

Studies of acute exposure to $LaCl_3$ administered intravenously demonstrate that this compound impairs clotting parameters in dogs and rabbits (Nagy et al., 1976; Graca et al., 1964). Nagano et al. (2000) reported increased testicular calcium concentrations in mice given a single i.v. dose of $LaCl_3$, but no effects on testes weight or histology were seen. No other studies examining potential male reproductive effects of soluble lanthanum salts were located.

Liver lesions were observed in several studies of rats, mice, and rabbits exposed to $LaCl_3$ by i.p. or i.v. injection (Fei et al., 2011; Kádas et al., 1974; Kádas et al., 1973; Kádas and Jobst, 1973). In mice, the lesions consisted of hepatocyte basophilia and central vein congestion (Fei et al., 2011). In rats and rabbits, the effects were described as "diffuse cellular lesions" or "specific necrobiosis" (Kádas et al., 1974; Kádas et al., 1973; Kádas and Jobst, 1973). Using electron microscopy, Kádas et al. (1974) further characterized the diffuse cellular lesions as enlarged nucleoli, irregularly shaped aggregates of glycogen granules or scarce glycogen granules, and focal areas of vesicular transformation of rough ER; the "specific necrobiosis" changes were seen on electron microscopy as swollen centrilobular cells, decreased rough ER and increased

vesicular-type ER, increased numbers of mitochondria with decreased electron density and partially destroyed cristae, and swollen biliary epithelium.

A study of intratracheal instillation showed signs of toxicity in bronchoalveolar lavage fluid (BALF) and an inflammatory response (increased eosinophils) in the lungs of rats exposed to $LaCl_3$ at a dose of 50 µg La/rat (Suzuki et al., 1992). After intranasal instillation of $LaCl_3$ at a dose of 1 mg La/kg for 6 months, lung lesions were observed in exposed mice, along with increased markers of oxidative stress in the lung (Hong et al., 2015). A shorter duration of exposure (14 days at 11 mg La/kg-day) by this route also resulted in evidence for oxidative stress in the lungs (increased lipid peroxidation) (Li et al., 2010).

Developmental toxicity was observed in mice exposed by i.p. injection to 44 mg La/kg (as $LaCl_3$) on a single day during gestation (Abramczuk, 1985). Exposure on GDs 4, 14, or 16 decreased the fraction of females continuing pregnancy and the average litter size. Exposure on GD 6 decreased the fraction of females continuing pregnancy without affecting litter size, while exposure on GD 12 decreased litter size without affecting pregnancy continuation. Finally, exposure on GD 4 also decreased the number of females with at least one implantation site and the average number of implantation sites per pregnant female on GD 5 (Abramczuk, 1985).

The potential neurotoxicity of $LaCl_3$ has been examined in rats and chickens exposed by injection routes. In rats, i.p. exposure to $LaCl_3$ increased brain AChE activity and increased oxidative stress in the brain (Liapi et al., 2009). After subcutaneous (s.c.) injection of $LaCl_3$ to dams during pregnancy, rat pups exhibited a temporary delay in swimming behavior that was no longer evident by PND 22 (Wadkins et al., 1998). Intracranial injection of $LaCl_3$ in rats inhibited responses in tail flick and hot plate tests (Harris et al., 1975), and inhibited the increase in motor activity induced by i.p. injection of cocaine (Kuzmin and Zwartau, 1996). Neurobehavioral effects (decreased mean avoidance rate in passive avoidance learning task, delays in response latency in tests of detour learning, or transient memory loss) were seen in chickens exposed by injection into embryonic eggs (Che et al., 2009) or intracranial injection (Che et al., 2011; Summers et al., 1996).

Mode-of-Action/Mechanistic Studies

Target organs or systems identified in oral toxicity studies of soluble lanthanum salts include the nervous system (including olfaction), liver, kidney, bone, and lung (see Table 3A). Based on the identified LOAELs in Table 3A, the most sensitive organ or systems are the nervous system, kidney, and bone. In the single study identifying renal effects of $LaCl_3$ (Zhao et al., 2013), oxidative stress was increased in the kidney at doses that also induced kidney lesions, suggesting that induction of oxidative stress may be involved in the mechanism of kidney toxicity. No other information on mechanisms of kidney toxicity were located.

The effects of lanthanum on bone composition may relate to the element's similarity to calcium in ionic radius and/or its ability to sequester phosphate via formation of insoluble lanthanum phosphate (Huang et al., 2006). In addition to being similar in ionic radius to calcium (and thus able to substitute for calcium in bone), lanthanum is known to block calcium channels that may be involved in critical signaling during bone remodeling (Huang et al., 2006). In vitro studies have shown that exposure to $LaCl_3$ can affect osteoblast and osteoclast proliferation, differentiation, and/or mineralization (Jiang et al., 2016; Liu et al., 2012; Wang et al., 2008; Zhang et al., 2007).

Lanthanum's effects on the central nervous system (CNS) may also stem from its ability to interfere with calcium homeostasis. Zarros et al. (2013) reviewed mechanistic data and outlined plausible mechanistic pathways for lanthanum-induced effects on cognitive function and the hippocampus. As described by these study authors, effects on spatial learning and memory are initiated by translocation of lanthanum into hippocampal cells via calcium gateways, leading to displacement of intracellular calcium from its binding sites. Calcium displacement generates mitochondrial dysfunction and oxidative stress, leading to the cells' failure to maintain long-term potentiation (believed to play a role in long-term storage of spatial and contextual memories) and triggering apoptosis. Lanthanum may also exert neurotoxic effects by interfering with the calcium-calmodulin complex, leading to decreased activation of Ca^{2+} calmodulin-dependent protein kinases that regulate transcription and translation in Nissl bodies of genes, necessary for synaptic consolidation and long-term potentiation (Zarros et al., 2013). Other studies (Jin et al., 2017; Zhang et al., 2017) also suggested that perturbation of the Nrf2-antioxidant response element signaling pathway or suppression of astrocyte-neuron lactate shuttle may also be responsible for the impaired spatial learning and memory of rats.

Metabolism/Toxicokinetic Studies

The oral absorption of lanthanum and other lanthanide elements is very low, in part because these elements form insoluble hydroxides at neutral pH. While an estimate of the gastrointestinal (GI) absorption of lanthanum 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 lanthanum 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 lanthanum concentrations were in the lung (448 nmol/kg fresh weight), liver (248 nmol/kg), and rib (194 nmol/kg), followed by stomach (109 nmol/kg), small intestine (103 nmol/kg), thyroid (94 nmol/kg), and heart (86 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 high variability in the measured concentrations. Distribution of lanthanum after oral exposure was reported in a study of male Wistar rats exposed to lanthanum chloride in drinking water (Rabinowitz et al., 1988). After 1 day of exposure to $^{140}LaCl_3$ at a dose estimated by the study authors as 0.77−0.9 mmol $LaCl_3$/kg-day (~100−125 mg La/kg-day), the highest tissue concentrations of radioactivity were in the intestine, lung, kidney, liver, and tongue muscle (see Table 5). In rats exposed for 2 or 3 days, concentrations of ^{140}La in soft tissues remained fairly constant, while concentrations in the bone and teeth increased. The study authors suggested that the soft tissues quickly reached a dynamic equilibrium, while bone and teeth continued to absorb lanthanum. Using acid washes of the teeth, the investigators demonstrated that the highest lanthanum concentration was in the surface of the teeth; 50% of the lanthanum in teeth was removed by four acid washes that dissolved only 1% of the tooth weight. This finding suggests that lanthanum was deposited on the teeth during intake of the drinking water, rather than through

systemic distribution. Rabinowitz et al. (1988) also evaluated the fractional distribution of ^{140}La in the liver of exposed rats. After either 1 or 2 days of exposure, most of the radioactivity was found in the soluble fraction of the liver (62−68% of liver radioactivity), with lesser amounts in the membranes (21−26%), mitochondria (99−10%), and nuclei (~2%).

Table 5. Tissue Distribution of ^{140}La after Administration of $LaCl_3$ in Drinking Water to Male Wistar Rats[a, b]

Tissue	Concentration of ^{140}La (nmol La/g Tissue) after 1, 2, or 3 d of Exposure		
	1 d	2 d	3 d
Ileum	36 ± 30	38 ± 5	29 ± 4
Lung	35 ± 10	24 ± 6	33 ± 8
Kidney	24 ± 8	27 ± 3	23 ± 2
Liver	23 ± 7	18 ± 8	23 ± 8
Spleen	13 ± 2	15 ± 3	12 ± 1
Femur bone	13 ± 5	16 ± 5	27 ± 5
Incisor tooth	12 ± 4	24 ± 3	55 ± 6
Tongue muscle	22 ± 3	25 ± 4	29 ± 5
Heart muscle	8 ± 4	12 ± 4	6 ± 2
Leg muscle	7 ± 3	9 ± 3	8 ± 2
Brain	2 ± 1	1 ± 1	1 ± 1

[a]Rabinowitz et al. (1988).
[b]Mean ± SEM.

La = lanthanum; $LaCl_3$ = lanthanum (III) chloride; SEM = standard error of the mean.

Toxicity studies that evaluated the distribution of lanthanum after oral exposure of rats to lanthanum chloride showed dose-related increases in tissue concentrations of lanthanum after both gavage (Feng et al., 2006b; Ogawa, 1992) and drinking water exposure (Liu et al., 2014; Yang et al., 2013; Hao et al., 2012; Yang et al., 2009). In a 28-day study that measured lanthanum in several tissues (Ogawa, 1992), concentrations were highest in the liver (~2−5 µg/g dry weight based on data shown graphically), followed by kidney (≤1 µg/g), and bone and spleen (~<0.5 µg/g). Neurodevelopmental studies provided evidence that lanthanum crossed the blood-brain barrier; levels up to ~0.06 µg/g have been measured in the hippocampus (Liu et al., 2014; Yang et al., 2013; Yang et al., 2009; Feng et al., 2006b). In addition, one study (Hao et al., 2012) demonstrated deposition of lanthanum in the olfactory bulb (18.5 ng/g compared with 2.3 ng/g in controls).

Male S-D rats (10/group) received a single intragastric dose of 10 mg $LaCl_3$. Two rats/group were sacrificed 1 hour, 6 hours, 24 hours, 2 days, or 3 days after dosing for examination of the distribution of lanthanum in the intestinal barrier (Floren et al., 2001). Results were described generally for several soluble lanthanide compounds similarly tested. Submicroscopic precipitates, primarily in the apical portion of the duodenum, were seen up to

2 days after dosing. After 3 days, no precipitate was seen. These data demonstrate that soluble lanthanide compounds precipitate in the proximal part of the intestinal tract.

Cuddihy and Boecker (1970) examined the kinetics of ^{140}La elimination after gavage, inhalation, and i.v. injection exposure of male and female beagle dogs to lanthanum chloride. After a single gavage dose of 25 mg ^{140}La, whole-body radioactivity declined rapidly during the first 2 days (to ~0.1% of the initial body burden) and more slowly for the remaining 6 days of observation (to ~0.015% of initial body burden). In contrast, after i.v. (0.25 mg ^{140}La) exposure, whole-body radioactivity declined slowly but steadily over the 8-day observation to ~2−5% of initial body burden. Data on inhalation exposure were from an experiment in which the dogs were exposed to a mixture of $^{140}LaCl_3$ and cesium chloride; the kinetics of elimination were like that seen with i.v. injection exposure. After inhalation exposure to the mixture, the highest concentrations of ^{140}La were found in the nasal turbinates, followed by lung, GI tract, liver, bones, and bronchial lymph nodes.

After i.v. exposure to 0.03 mg/kg-day lanthanum chloride in rats for 28 consecutive days, the liver, femur, kidney, and heart had concentrations of 2,593, 1,627, 231, and 96 ng/g tissue, respectively (Damment et al., 2009). The concentration of lanthanum in the skin was reported to be ≤160 ng/g; in the brain, the concentration was close to the limit of quantitation (~2−11 ng/g).

Long-term retention of lanthanum has not been studied; however, Durbin et al. (1956) measured retention of cerium (a lanthanide close to lanthanum in the series) in the skeleton over 256 days, and observed a two-phased elimination curve. The study authors reported that about one-third of the skeletal cerium was labile, with a half-life of about 15 days, while the remaining two-thirds was retained at the same level throughout the remaining 8 months. If lanthanum behaves similarly, a portion of skeletal lanthanum will be rapidly eliminated while the remainder persists unchanged.

No data were found on the excretion of soluble lanthanum salts after exposure of humans or animals. After oral administration of other lanthanide elements (yttrium, dysprosium, europium, and ytterbium, as their chloride hexahydrates) to male Wistar rats, none of these elements was detected in urine, and 92−98% of administered doses (100 and 1,000 mg lanthanide elements/kg) was excreted in the feces within 7 days [Nakamura et al. (1991); published in Japanese with English abstract and tables]. Excretion of orally administered lanthanum chloride is likely to follow a similar pattern. In rats exposed intravenously to lanthanum chloride (0.3 mg/kg), the majority of the administered dose (74%) was excreted in the feces over 42 days, and <2% was excreted in urine (Damment and Pennick, 2007). In an experiment using bile duct-cannulated rats exposed to the same dose, 10% of the administered dose was excreted in bile over the 5 days during which bile was collected (Damment and Pennick, 2007).

DERIVATION OF PROVISIONAL VALUES

There are no data to derive reference values for lanthanum metal. Tables 6 and 7 present summaries of noncancer and cancer references values, respectively, for soluble lanthanum compounds.

Table 6. Summary of Noncancer Reference Values for Soluble Lanthanum

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg La/kg-d)	Rat/M	Decreased number of pyramidal cells in hippocampus	5×10^{-5}	BMDL	0.016	300	He et al. (2008)
Chronic p-RfD (mg La/kg-d)	Rat/M	Decreased number of pyramidal cells in hippocampus	5×10^{-5}	BMDL	0.016	300	He et al. (2008)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

BMDL = benchmark dose lower confidence limit; La = lanthanum; M = male(s); NDr = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; UF_C = composite uncertainty factor.

Table 7. Summary of Cancer Reference Values for Soluble Lanthanum

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

Studies pertinent to the derivation of a subchronic provisional reference dose (p-RfD) for soluble lanthanum include a 18-day study of dietary lanthanum chloride in rats (He et al., 2003), a 4-week rat gavage study of lanthanum chloride published in Japanese (Ogawa, 1992), a 3-month mouse gavage study of lanthanum chloride examining renal endpoints (Zhao et al., 2013), a 3-month rat gavage study of lanthanum nitrate (Fang et al., 2018), three 5~6-month studies of rats exposed by gavage to lanthanum chloride (Feng et al., 2006b) or lanthanum nitrate (Huang et al., 2006; Chen et al., 2003), and 11 studies of rats or mice exposed during premating, gestation, lactation, and/or postnatally to lanthanum chloride either in drinking water (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Hao et al., 2012; Yang et al., 2009; Briner et al., 2000) or by gavage (He et al., 2008; Feng et al., 2006a). The neurodevelopmental study by He et al. (2008) is selected as the principal study for deriving a subchronic p-RfD for soluble lanthanum salts, as described below.

Justification of the Critical Effect

A number of studies (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Yang et al., 2009; He et al., 2008; Feng et al., 2006a; Feng et al., 2006b; Briner et al., 2000) have identified the CNS as a sensitive target of lanthanum chloride exposure, with LOAELs as low as 1 mg La/kg-day (He et al., 2008). These studies identify a consistent pattern of impaired spatial learning and memory, as measured by Morris water maze performance. The neurobehavioral changes are supported by findings of morphological and histological changes in the hippocampus, the part of the brain involved in memory and navigation. Gestational and/or postnatal exposure to lanthanum chloride was observed to result in decreased numbers of hippocampal pyramidal cells, neural degeneration, and alterations in the morphology of hippocampal synapses (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Yang et al., 2009; He et al., 2008). The neurodevelopmental studies in particular provide both functional and structural evidence of neurotoxicity. In addition, several of these studies evaluated mechanistic endpoints providing additional evidence for the relationship between exposure to lanthanum chloride and neurotoxicity as discussed in the "Mode-of-Action/Mechanistic Studies" section.

There is some evidence for an effect of soluble lanthanum salts on the liver, albeit at higher doses than the most sensitive measures of CNS impairment. Hepatic lesions (inflammatory lesions and disturbances of the hepatocyte cord arrangements) were observed at 7.26 mg La/kg-day in a 6-month study of rats (Chen et al., 2003). The lesions were accompanied by a twofold increase in serum ALP at the same dose, although no changes in ALT, AST, or GGT were observed. Fang et al. (2018) reported increases in serum ALT (55%) and AST (38%) in female rats exposed to 61.6 mg La/kg-day for 3 months. He et al. (2003) observed a 50% increase in serum ALP and a twofold increase in serum ALT in rats exposed to 5.17 mg La/kg-day for 18 days. Ogawa (1992) found significant increases in serum ALT and AST at 374 mg La/kg-day in rats treated by gavage for 28 days. Additional support for the liver as a target of lanthanum toxicity is available in short-term-duration studies of mice (Fei et al., 2011) and rats (Kádas et al., 1974; Kádas et al., 1973; Kádas and Jobst, 1973) exposed by injection routes (see Table 4B). Other effects of lanthanum chloride exposure reported in the available studies include decreased body weight (Jin et al., 2017; Zhang et al., 2017; Feng et al., 2006a) and impaired olfactory function (Hao et al., 2012). These effects occurred at doses ≥20 mg La/kg-day, so these endpoints were not considered the most sensitive effects for use in deriving the provisional reference values.

Justification of the Principal Study

Among the studies that identified neurobehavioral and neurodevelopmental effects of lanthanum chloride exposure (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Yang et al., 2009; He et al., 2008; Feng et al., 2006a; Feng et al., 2006b; Briner et al., 2000), gavage administration was used in three studies (He et al., 2008; Feng et al., 2006a; Feng et al., 2006b), while the remaining studies (Jin et al., 2017; Zhang et al., 2017; Liu et al., 2014; Yang et al., 2013; Zheng et al., 2013; Yang et al., 2009; Briner et al., 2000) used drinking water administration. The drinking water studies identified LOAELs that were higher (115.3−308.6 mg La/kg-day) than those identified in gavage studies (1−23 mg La/kg-day). None of the drinking water studies identified a NOAEL, but the LOAELs are too high to consider as the basis for the p-RfD point of departure (POD). In contrast, both Feng et al. (2006a) and He et al. (2008) identified both LOAELs and NOAELs in a much lower range.

For the study by Feng et al. (2006a), a LOAEL of 23 mg La/kg-day was identified for decreased body weight, decreased swimming endurance, and increased escape latency in the Morris water maze; the NOAEL was 1 mg La/kg-day. For the study by He et al. (2008), a LOAEL of 1 mg La/kg-day and NOAEL of 0.06 mg La/kg-day were identified for increased general path length and decreased preference for target quadrant in the Morris water maze, as well as decreased numbers of pyramidal cells in the hippocampus. Although decreased body weight could potentially influence the outcome of behavioral tasks, body weights of the pups were not affected by exposure to lanthanum chloride for 6 months. Thus, the observed neurobehavioral changes in He et al. (2008) were not likely to be confounded by effects on body weight. The study by He et al. (2008) identified a lower, more sensitive LOAEL and was therefore selected as the principal study for neurobehavioral effects.

Approach for Deriving the Subchronic p-RfD

The most sensitive neurodevelopmental endpoints in the principal study were two measures of performance in the Morris water maze (length of pathway to platform and preference for the target quadrant) and the numbers of pyramidal cells in the CA3 region of the hippocampus. All endpoints were subjected to benchmark dose (BMD) modeling to identify candidate PODs for deriving the subchronic p-RfD (see Appendix C), and the dose-response data are presented in Table B-14.

Candidate PODs, including BMDs and benchmark dose lower confidence limits (BMDLs), resulting from the best-fitting models of data from He et al. (2008) are shown in Table 8.

Table 8. Candidate PODs for the Subchronic p-RfD for Soluble Lanthanum

Endpoint[a]	Dose (mg La/kg-d)				BMR
	NOAEL	LOAEL	BMD	BMDL	
Decreased number of pyramidal cells in CA3 area of hippocampus (number/mm^2)	0.06	1	0.083	0.016	1 SD
Increased length general path in Morris water maze (cm)	0.06	1	2.46	0.70	1 SD
Decreased preference for target quadrant in Morris water maze (percentage of time spent in target quadrant)	0.06	1	0.93	0.11	1 SD

[a]He et al. (2008).

BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; BMR = benchmark response; La = lanthanum; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfD = provisional reference dose; SD = standard deviation.

The lowest candidate POD was the BMDL for decreased number of pyramidal cells in the hippocampus (He et al., 2008); this value (0.016 mg La/kg-day) is selected as the POD for the subchronic p-RfD. The BMDL was not converted to a human equivalent dose (HED), as such a conversion is not appropriate when neonatal and/or juvenile animals are directly exposed to the test chemical.

The subchronic p-RfD for soluble lanthanum is derived using the POD of 0.016 mg La/kg-day and a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 10, an intraspecies uncertainty factor [UF_H] of 10, and a database uncertainty factor [UF_D] of 3):

Subchronic p-RfD	=	POD ÷ UF_C
for Soluble Lanthanum	=	0.016 mg La/kg-day ÷ 300
	=	**5×10^{-5} mg La/kg-day**

Table 9 summarizes the uncertainty factors for the subchronic p-RfD for soluble lanthanum.

Table 9. Uncertainty Factors for the Subchronic p-RfD for Soluble Lanthanum

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans.
UF_D	3	A UF_D of 3 is applied to account for deficiencies in the toxicity database for soluble lanthanum salts. The database includes 3-, 5- and 6-mo studies (Zhao et al., 2013; Feng et al., 2006b; Huang et al., 2006; Chen et al., 2003) that examined comprehensive toxicity endpoints. The database also includes several developmental studies, but none has examined teratogenicity. Furthermore, no studies have examined reproductive endpoints.
UF_H	10	A UF_H of 10 is applied to account for intraspecies variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; 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.

Confidence in the subchronic p-RfD for soluble lanthanum is low as described in Table 10.

Table 10. Confidence Descriptors for the Subchronic p-RfD for Soluble Lanthanum

Confidence Categories	Designation	Discussion
Confidence in principal study	M	Confidence in the principal study is medium. He et al. (2008) is a peer-reviewed study using three nonzero dose groups of 10 dams/dose. The study investigated both structural (number of pyramidal cells in the hippocampus) and functional (Morris water maze performance) measures of neurodevelopment, and both LOAEL and NOAEL doses were identified. Deficiencies in the study include the lack of information on litter distribution of the offspring selected for testing in the Morris water maze and the small numbers of offspring (4/group) examined for number of pyramidal cells in the hippocampus.
Confidence in database	M	Confidence in the database is medium. The database for soluble lanthanum salts includes 18-d, 28-d, and 3-, 5- or 6-mo studies in rats, a 90-d study in mice, 10 developmental studies in rats examining neurodevelopmental and olfactory endpoints, and a single neurodevelopmental study in mice. There are no studies of potential teratogenicity in humans or animals exposed orally, although an i.p. study (Abramczuk, 1985) showed effects on pregnancy maintenance and litter size. Standard developmental toxicity studies of soluble lanthanum salts are needed. Furthermore, no studies have examined reproductive endpoints.
Confidence in subchronic p-RfD[a]	M	Overall confidence in the subchronic p-RfD is medium.

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

i.p. = intraperitoneal; L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfD = provisional reference dose.

Derivation of a Chronic Provisional Reference Dose

No studies of soluble lanthanum with exposure duration longer than 6 months have been identified in the literature. Therefore, the POD for neurodevelopmental effects in the study by He et al. (2008) is selected as the basis for the chronic p-RfD. Because the principal study included gestational exposure, an uncertainty factor for duration extrapolation was not included. Therefore, the **chronic p-RfD for soluble lanthanum (5×10^{-5} mg La/kg-day)** is the same as the subchronic p-RfD. The uncertainty factors for the chronic p-RfD are the same as those shown in Table 9.

The chronic p-RfD for soluble lanthanum was derived using the POD of 0.016 mg La/kg-day and a UF_C of 300 (reflecting a UF_A of 10, a UF_H of 10, and a UF_D of 3):

$$\begin{aligned} \textbf{Chronic p-RfD} &= \text{POD} \div UF_C \\ \textbf{for Soluble Lanthanum} &= 0.016 \text{ mg La/kg-day} \div 300 \\ &= \mathbf{5 \times 10^{-5} \text{ mg La/kg-day}} \end{aligned}$$

Table 11 summarizes the uncertainty factors for the chronic p-RfD for soluble lanthanum salts.

Table 11. Uncertainty Factors for the Chronic p-RfD for Soluble Lanthanum Salts

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans.
UF_D	3	A UF_D of 3 is applied to account for deficiencies in the toxicity database for soluble lanthanum salts. The database includes 3-, 5- and 6-mo studies (Zhao et al., 2013; Feng et al., 2006b; Huang et al., 2006; Chen et al., 2003) that examined comprehensive toxicity endpoints. The database also includes several developmental studies, but none has examined teratogenicity. Furthermore, there are no studies of reproductive endpoints.
UF_H	10	A UF_H of 10 is applied to account for intraspecies variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of in humans.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL.
UF_S	1	A UF_S of 1 is applied because a developmental study was selected as the principal study.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limit; 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.

Confidence in the chronic p-RfD for soluble lanthanum is medium as described in Table 12.

Table 12. Confidence Descriptors for the Chronic p-RfD for Soluble Lanthanum Salts

Confidence Categories	Designation	Discussion
Confidence in principal study	M	Confidence in the principal study is medium. He et al. (2008) is a peer-reviewed study using three nonzero dose groups of 10 dams/dose. The study investigated both structural (number of pyramidal cells in the hippocampus) and functional (Morris water maze performance) measures of neurodevelopment, and both LOAEL and NOAEL doses were identified. Deficiencies in the study include the lack of information on litter distribution of the offspring selected for testing in the Morris water maze and the small numbers of offspring (4/group) examined for number of pyramidal cells in the hippocampus.
Confidence in database	M	Confidence in the database is medium. The database for soluble lanthanum salts includes 18-d, 28-d, and 3-, 5- or 6-mo studies in rats, a 90-d study in mice, 10 developmental studies in rats examining neurodevelopmental and olfactory endpoints, and a single neurodevelopmental study in mice. There are no studies of potential teratogenicity in humans or animals exposed orally, although an i.p. study (Abramczuk, 1985) showed effects on pregnancy maintenance and litter size. Standard developmental toxicity studies of soluble lanthanum salts are needed. Furthermore, no studies have examined reproductive endpoints.
Confidence in chronic p-RfD[a]	M	Overall confidence in the chronic p-RfD is medium.

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

i.p. = intraperitoneal; L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; p-RfD = provisional reference dose.

Because the fundamental determinant of the toxicity of soluble lanthanum compounds is expected to be due to lanthanum metal itself, the toxicity of such soluble compounds is directly related to the relative molecular weight contribution from lanthanum. Therefore, the subchronic and chronic p-RfDs derived above for soluble lanthanum are applicable to soluble lanthanum compounds (e.g., salts) following application of a molecular-weight adjustment and appropriate stoichiometric calculations.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

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

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No carcinogenicity data have been located for soluble lanthanum. Genotoxicity studies of lanthanum chloride, lanthanum nitrate, and lanthanum acetate are available; these studies are limited, but available data suggest that lanthanum nitrate may be genotoxic in human lymphocytes (Yongxing et al., 2000). The cancer weight-of-evidence (WOE) descriptor for soluble lanthanum salts is *"Inadequate Information to Assess Carcinogenic Potential"* as presented in Table 13.

Table 13. Cancer WOE Descriptor for Soluble Lanthanum

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 carcinogenicity effects in humans or animals exposed to soluble lanthanum.**
"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 lanthanum is precluded by the lack of data demonstrating carcinogenicity associated with exposure to soluble lanthanum.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are derived.

APPENDIX B. DATA TABLES

Table B-1. Serum Chemistry Changes in Wistar Rats Exposed to Lanthanum Chloride Hexahydrate in the Diet for 18 Days[a, b]

Endpoint	Dose (mg La/kg-d)		
	0	**2.6**	**5.17**
ALT (U/L)	24.4	44.3* (82)	57* (134)
ALP (U/L)	209	254 (22)	328* (57)

[a]He et al. (2003).
[b]Data reported as mean (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 10/group.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; La = lanthanum.

Table B-2. Selected Clinical Chemistry Results in Slc:Wistar Rats Exposed to Lanthanum Chloride Heptahydrate by Gavage for 28 Days[a, b]

Endpoint	Dose (mg La/kg-d)						
	Groups Sacrificed after Exposure					Recovery Groups	
	0	15	74.8	374	Pair-Fed Control	0	374
Male							
Total protein (g/dL)	6.3 ± 0.09	6.23 ± 0.1 (−1.1)	6.04 ± 0.25 (−4.1)	5.69 ± 0.23**, # (−9.7)	5.98 ± 0.12** (−5.1)	6.38 ± 0.08	6.13 ± 0.15* (−3.9)
BUN (mg/dL)	20.1 ± 2.7	20.1 ± 2 (0)	18.2 ± 1.8 (−9.5)	18.6 ± 3.6## (−7.5)	12.6 ± 0.7** (−37)	20.5 ± 2.5	20.8 ± 1.7 (+1.5)
Creatinine (mg/dL)	0.42 ± 0.02	0.42 ± 0.02 (0)	0.44 ± 0.05 (+4.8)	0.44 ± 0.07 (+4.8)	0.43 ± 0.03 (+2.4)	0.47 ± 0.04	0.41 ± 0.05 (−12.8)
Uric acid (mg/dL)	0.95 ± 0.18	1.14 ± 0.4 (+20)	1.1 ± 0.2 (+15.8)	1.05 ± 0.35 (+10.5)	0.7 ± 0.12* (−26)	0.74 ± 0.22	0.73 ± 0.06 (−1.4)
ALT (mU/mL)	48 ± 2	51 ± 5 (+6.3)	58 ± 6* (+20.8)	105 ± 34*, # (+118.8)	41 ± 7 (−15)	52 ± 7	55 ± 9 (+5.8)
AST (mU/mL)	75 ± 4	75 ± 3 (0)	80 ± 5 (+6.7)	98 ± 12**, ## (+30.7)	68 ± 9 (−9.3)	74 ± 11	75 ± 13 (+1.4)
Cholinesterase (mU/mL)	172 ± 26	156 ± 7 (−9.3)	174 ± 18 (+1.2)	168 ± 14 (−2.3)	195 ± 33 (+13)	147 ± 14	197 ± 16** (+34)
Female							
Total protein (g/dL)	5.95 ± 0.11	5.89 ± 0.11 (−1)	5.87 ± 0.28 (−1.3)	5.27 ± 0.24**, # (−11.4)	5.62 ± 0.05** (−5.5)	6.24 ± 0.13	6.21 ± 0.1 (−0.5)
BUN (mg/dL)	18.8 ± 2.4	18.2 ± 1.8 (−3.2)	16.6 ± 1.8 (−11.7)	17.2 ± 3.9## (−8.5)	10.6 ± 0.8** (−44)	16 ± 0.9	17 ± 1.2 (+6.3)
Creatinine (mg/dL)	0.64 ± 0.04	0.65 ± 0.02 (+1.6)	0.6 ± 0.07 (−6.3)	0.61 ± 0.02## (−4.7)	0.48 ± 0.04** (−25)	0.51 ± 0.04	0.47 ± 0.02* (−7.8)
Uric acid (mg/dL)	0.74 ± 0.09	1.00 ± 0.18* (+35.1)	0.96 ± 0.14* (+29.7)	1.03 ± 0.2*, ## (+39.2)	0.51 ± 0.08** (−31)	0.49 ± 0.11	0.64 ± 0.14 (+30.6)
ALT (mU/mL)	47 ± 10	52 ± 7 (+10.6)	44 ± 4 (−6.4)	72 ± 7**, ## (+53.2)	35 ± 5 (−26)	43 ± 9	49 ± 13 (+14)

Table B-2. Selected Clinical Chemistry Results in Slc:Wistar Rats Exposed to Lanthanum Chloride Heptahydrate by Gavage for 28 Days[a, b]

Endpoint	Dose (mg La/kg-d)						
	Groups Sacrificed after Exposure					Recovery Groups	
	0	15	74.8	374	Pair-Fed Control	0	374
AST (mU/mL)	82 ± 4	79 ± 2 (−3.7)	90 ± 11 (+9.8)	92 ± 5**, ## (+12.2)	76 ± 9 (−7.3)	69 ± 8	75 ± 6 (+8.7)
Cholinesterase (mU/mL)	1,022 ± 89	1,001 ± 196 (−2.1)	760 ± 150** (−25.6)	348 ± 34**, ## (−65.9)	651 ± 94** (−36)	1,275 ± 149	976 ± 195* (−23.5)

[a]Ogawa (1992).
[b]Data reported as mean ± SD (percent change compared with untreated control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 4 or 5/group.
*Statistically significantly different from untreated control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from untreated control ($p \leq 0.01$), as reported by the study authors.
#Statistically significantly different from pair-fed control ($p \leq 0.05$), as reported by the study authors.
##Statistically significantly different from pair-fed control ($p \leq 0.01$), as reported by the study authors.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; La = lanthanum; SD = standard deviation.

Table B-3. Selected Histopathology Results in Slc:Wistar Rats Exposed to Lanthanum Chloride Heptahydrate by Gavage for 28 Days[a, b]

Endpoint	Dose (mg La/kg-d)					
	Groups Sacrificed after Exposure				Recovery Groups	
	0	15	74.8	374	0	374
Male						
Lung granulation	0/5	0/5	4/5*	4/5*	0/5	2/4
Lung giant cell appearance	0/5	0/5	4/5*	4/5*	0/5	2/4
Lung eosinocyte infiltration	0/5	0/5	2/5	3/5	0/5	0/4
Lung alveolar wall thickening	0/5	1/5	0/5	0/5	0/5	0/4
Stomach (forestomach) hyperkeratosis	0/5	0/5	0/5	2/5	0/5	0/4
Stomach (glandular) erosion	0/5	0/5	0/5	3/5	0/5	0/4
Stomach (glandular) dilatation of acinus	0/5	0/5	0/5	4/5*	0/5	0/4
Stomach (glandular) epithelium swelling	0/5	0/5	0/5	0/5	0/5	0/4
Stomach (submucosa) eosinocyte infiltration	0/5	0/5	0/5	4/5*	0/5	0/4
Female						
Lung granulation	0/5	1/5	5/5**	1/5	0/5	3/5
Lung giant cell appearance	0/5	1/5	4/5*	1/5	0/5	2/5
Lung eosinocyte infiltration	0/5	0/5	2/5	0/5	0/5	0/5
Lung alveolar wall thickening	0/5	2/5	0/5	4/5*	0/5	0/5
Stomach (forestomach) hyperkeratosis	0/5	1/5	1/5	5/5**	0/5	1/5
Stomach (glandular) erosion	0/5	0/5	0/5	0/5	0/5	1/5
Stomach (glandular) dilatation of acinus	0/5	0/5	0/5	0/5	0/5	0/5
Stomach (glandular) epithelium swelling	0/5	0/5	0/5	4/5*	0/5	0/5
Stomach (submucosa) eosinocyte infiltration	0/5	0/5	0/5	5/5**	0/5	0/5

[a]Ogawa (1992). Data for pair-fed controls were not reported.
[b]Data reported as incidence (number affected/number examined).
*Statistically significantly different from untreated control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from untreated control ($p \leq 0.01$), as reported by the study authors.

La = lanthanum.

Table B-4. Serum Chemistry Changes in Male ICR Mice Exposed to Lanthanum Chloride by Gavage for 90 Days[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	1	3	5.7
Uric acid (µmol/L)	222.56 ± 11.13	160.21 ± 8.01* (−28)	110.88 ± 5.54** (−50.2)	96.76 ± 4.84*** (−56.5)
Creatinine (µmol/L)	8.81 ± 0.44	9.75 ± 0.49[c] (+10.7)	11.68 ± 0.58** (+32.6)	13.19 ± 0.66*** (+49.7)
BUN (mmol/L)	9.28 ± 0.46	8.11 ± 0.41[c] (−2.1)	7.05 ± 0.35** (−14.9)	6.32 ± 0.32*** (−23.7)
Calcium (mmol/L)	2.79 ± 0.14	2.58 ± 0.13[c] (−7.5)	2.41 ± 0.12** (−13.6)	2.12 ± 0.11*** (−24)
Phosphorus (mmol/L)	3.68 ± 0.18	3.52 ± 0.18[c] (−4.3)	3.40 ± 0.17** (−7.6)	3.18 ± 0.16** (−13.6)

[a]Zhao et al. (2013).
[b]Data reported as mean ± SEM (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 5/group.
[c]Not statistically significantly different from control by t-test performed for this review. Positive statistical results reported by the study authors appeared suspect upon initial visual inspection and could not be subsequently duplicated.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

BUN = blood urea nitrogen; La = lanthanum; SEM = standard error of the mean.

Table B-5. Organ Weights of Male S-D Rats Exposed to Lanthanum Nitrate by Gavage for 90 Days[a, b]

Endpoint	Dose (mg La/kg-d)				
	0	0.64	2.6	10.3	61.6
Liver (g)	11.525 ± 0.96	11.208 ± 1.12 (−2.8)	10.765 ± 0.95 (−6.6)	10.576 ± 2.87 (−8.2)	8.494 ± 1.35* (−26)
Spleen (g)	0.810 ± 0.05	0.815 ± 0.10 (+0.6)	0.790 ± 0.15 (−2.4)	0.739 ± 0.79 (−8.8)	0.637 ± 0.17* (−21)
Kidney (g)	2.870 ± 0.20	2.876 ± 0.23 (+0.2)	2.861 ± 0.29 (−0.3)	2.718 ± 0.27 (−5.3)	2.250 ± 0.30* (−22)
Heart (g)	1.466 ± 0.11	1.495 ± 0.11 (+2.0)	1.508 ± 0.18 (+2.9)	1.386 ± 0.11 (−5.5)	1.210 ± 0.07* (−17)
Thymus (g)	0.370 ± 0.10	0.330 ± 0.07 (−11)	0.385 ± 0.10 (+4.1)	0.303 ± 0.07 (−18)	0.269 ± 0.07* (−27)

[a]Ogawa (1992).
[b]Data reported as mean ± SD (percent change compared with untreated control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 10/group.
*Statistically significantly different from untreated control ($p \leq 0.05$), as reported by the study authors.

La = lanthanum; SD = standard deviation; S-D = Sprague-Dawley.

Table B-6. Selected Clinical Chemistry Results in Female S-D Rats Exposed to Lanthanum Nitrate by Gavage for 90 Days[a, b]

Endpoint	Dose (mg La/kg-d)						
	Groups Sacrificed after Exposure					Recovery Groups	
	0	0.64	2.6	10.3	61.6	0	61.6
ALT (U/L)	21.0 ± 5.2	21.5 ± 5.7 (+0.1)	24.0 ± 6.5 (+14)	24.2 ± 6.6 (+15)	32.6 ± 9.9* (+55)	30 ± 4.65	34 ± 6.9 (+13)
AST (U/L)	65.8 ± 22.1	64.0 ± 20.9 (−2.7)	76.2 ± 13.8 (+16)	72.2 ± 18.2 (+9.7)	91.1 ± 17.8* (+38)	82.4 ± 4.1	98.2 ± 3.8 (+19)
Glucose (mmol/L)	5.7 ± 1.4	6.3 ± 0.6 (+11)	6.2 ± 1.0 (+8.7)	6.3 ± 1.3 (+11)	7.0 ± 0.8* (+23)	6.3 ± 1.3	6.9 ± 1.2 (+9.5)
Urea (mmol/L)	5.0 ± 0.7	5.1 ± 0.6 (+2.0)	5.4 ± 0.6 (+8.0)	5.8 ± 1.3 (+16)	6.4 ± 1.1* (+28)	6.4 ± 1.0	5.7 ± 0.8 (−11)
Creatinine (µmol/L)	28.8 ± 10.4	36.7 ± 11.2 (+27)	37.1 ± 8.9 (+29)	35.0 ± 12.2 (+22)	41.6 ± 9.2* (+44)	26.4 ± 5.6	24.3 ± 2.4 (−8.0)
Ca (mmol/L)	1.7 ± 0.4	1.7 ± 0.3 (0)	1.9 ± 0.4 (+12)	1.9 ± 0.3 (+12)	2.1 ± 0.3* (+24)	2.4 ± 0.02	2.3 ± 0.03 (−0.42)

[a]Ogawa (1992).
[b]Data reported as mean ± SD (percent change compared with untreated control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 10/group.
*Statistically significantly different from untreated control ($p \leq 0.05$), as reported by the study authors.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SD = standard deviation; S-D = Sprague-Dawley.

Table B-7. Neurotransmitter Concentrations in Brains of Male Wistar Rats Exposed to Lanthanum Chloride by Gavage for 5 Months[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	0.06	1	23
Dopamine (ng/g brain tissue)	503.1 ± 53.5	468.7 ± 81.2 (−6.8)	432.6 ± 131.8 (−14)	389.9 ± 74.6* (−22.5)
Dihydroxyphenylacetic acid (ng/g brain tissue)	180.2 ± 41.3	158.4 ± 37.2 (−12.1)	144.5 ± 26.3 (−19.8)	141.1 ± 30.1* (−21.7)
5-HT (ng/g brain tissue)	142.4 ± 34.7	115.1 ± 26.2 (−19.2)	109.7 ± 31.5* (−23)	109.9 ± 14.3* (−22.8)
Norepinephrine (ng/g brain tissue)	312.8 ± 44	305.5 ± 46.9 (−2.3)	271.5 ± 84.9 (−13.2)	224.7 ± 87.1* (−28.2)

[a]Feng et al. (2006b).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 10/group.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

5-HT = 5-hydroxytryptamine; La = lanthanum; SD = standard deviation.

Table B-8. Selected Results in Wistar Rats Exposed to Lanthanum Nitrate by Gavage for 6 Months[a, b]						
Endpoint	**Dose (mg La/kg-d)**					
	0	**0.036**	**0.073**	**0.73**	**3.63**	**7.26**
Male						
Relative liver weight[c] (%)	2.83 ± 0.55	3.06 ± 0.39 (+8.1)	2.99 ± 0.41 (+5.7)	2.8 ± 0.31 (−1.1)	2.44 ± 0.44 (−14)	3.03 ± 0.56 (7.1)
Serum ALP[d] (IU/L)	99.13 ± 27.51	177.65 ± 34.94*** (+79)	148.44 ± 52.86** (+50)	169.75 ± 53.64*** (+71)	123.11 ± 71.04 (+24)	221.17 ± 64.35*** (+123)
Female						
Relative liver weight[c] (%)	3.4 ± 0.28	2.65 ± 0.28* (−22.1)	3.69 ± 0.40 (+8.5)	3.54 ± 0.33 (+4.1)	3.54 ± 0.26 (+4.1)	3.65 ± 0.41 (+7.4)
Serum ALP[d] (IU/L)	162.02 ± 61.58	157.74 ± 28.43 (−2.6)	202.61 ± 39.27 (+25)	160.46 ± 41.48 (−1)	191.48 ± 59.80 (+18.2)	166.75 ± 34.64 (+2.9)

[a]Chen et al. (2003).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100.
[c]Group sizes were 13/dose.
[d]Group sizes were 13/dose.
*Statistically significantly different from control ($p < 0.05$), by *t*-test performed for this review. Negative statistical result reported by the study authors appeared suspect upon initial visual inspection and could not be subsequently duplicated.
**Statistically significantly different from control ($p < 0.01$), by *t*-test performed for this review.
***Statistically significantly different from control ($p < 0.001$), by *t*-test performed for this review.

ALP = alkaline phosphatase; La = lanthanum; SD = standard deviation.

Table B-9. Bone Mineral Composition in Male Wistar Rats Exposed to Lanthanum Nitrate by Gavage for 6 Months[a, b]

Endpoint	Dose (mg La/kg-d)	
	0	0.85
Calcium (%)	24.9 ± 0.6	22 ± 0.8* (−11.6)
Phosphorus (%)	11.4 ± 0.6	9.5 ± 0.4* (−16.7)
Ratio of Ca:P (molar)	1.69 ± 0.08	1.83 ± 0.11 (+8.3)
Carbonate (%)	4.4 ± 0.3	6.2 ± 0.4* (+40.9)
Mineral:matrix (w/w)	5 ± 0.3	4.5 ± 0.2* (−10)

[a]Huang et al. (2006).
[b]Data reported as mean ± SEM (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 10/group.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

Ca = calcium; La = lanthanum; P = phosphorus; SEM = standard error of the mean.

Table B-10. Olfactory Function in Offspring of Wistar Rats Exposed to Lanthanum Chloride by Drinking Water from GD 7 to PND 21[a, b]

Endpoint	Dose (mg La/kg-d)	
	0	230.6
Buried food pellet test latency		
Trial 1 (s)	45.01 ± 9.04	85.73 ± 13.18* (+90.5)
Trial 2 (s)	39.22 ± 6.37	66.30 ± 7.82* (+69)
Trial 3 (s)	36.6 ± 5.26	62.28 ± 6.09* (+70.2)
Visible food pellet (s)	20.43 ± 3.61	22.19 ± 3.88 (+8.6)
Olfactory maze test latency		
Trial 1 (s)	67.25 ± 6.12	93.07 ± 6.38* (+38.4)
Trial 2 (s)	53.36 ± 5.75	76.27 ± 5.97* (+42.9)
Trial 3 (s)	48.05 ± 5.27	70.12 ± 6.03* (+45.9)
Visible food pellet (s)	46.13 ± 5.31	49.04 ± 4.95 (+6.3)

[a]Hao et al. (2012).
[b]Data reported as mean ± SEM (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; n = 8/group.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

GD = gestation day; La = lanthanum; PND = postnatal day; SEM = standard error of the mean.

Table B-11. Brain- and Body-Weight Changes in Wistar Rat Pups Exposed to Lanthanum Chloride during Gestation and Lactation and via Drinking Water for 1 Month[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	230.6 (maternal) 307.5 (pup)	461 (maternal) 615 (pup)	923 (maternal) 1,230 (pup)
Body weight (g)	176.25 ± 15.29	164.38 ± 11.31 (−6.7)	147.38 ± 13.65* (−16.4)	120.75 ± 14.64* (−31.5)
Brain weight (g)	1.73 ± 0.09	1.56 ± 0.510 (−9.8)	1.41 ± 0.19* (−18.5)	1.19 ± 0.13* (−31.2)
Brain weight coefficient (%)	0.98 ± 0.04	0.95 ± 0.06 (−3.1)	0.96 ± 0.12 (−2)	1 ± 0.13 (+2)

[a]Zheng et al. (2013).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 8/group.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

La = lanthanum; SD = standard deviation.

Table B-12. Body-Weight and Brain Changes in Wistar Rat Pups Exposed to Lanthanum Chloride during Gestation and Lactation and via Drinking Water for 2 Months[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	115.3 (maternal) 153.7 (pup)	230.6 (maternal) 307.5 (pup)	461 (maternal) 615 (pup)
Body weight (g)	291.0 ± 27.0	260.2 ± 48.2 (−10.6)	257.0 ± 29.1 (−11.7)	241.9 ± 51.7* (−31.5)
Brain weight (g)	1.78 ± 0.082	1.66 ± 0.119* (−6.7)	1.65 ± 0.82* (−7.3)	1.62 ± 0.87* (−9.0)
Brain coefficient (%)	0.614 ± 0.038	0.650 ± 0.067	0.646 ± 0.054	0.676 ± 0.102
Hippocampus weight (g)	0.124± 0.013	0.115 ± 0.017 (−7.3)	0.115 ± 0.007 (−7.3)	0.113 ± 0.151 (−8.9)
Hippocampus coefficient (%)	0.043± 0.004	0.044 ± 0.003	0.045 ± 0.005	0.047 ± 0.005

[a]Zhang et al. (2017).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 10/group.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.

La = lanthanum; SD = standard deviation.

Table B-13. Selected Results in Wistar Rat Offspring Exposed to Lanthanum Chloride by Gavage throughout Gestation and Lactation and by Gavage from PND 20 until up to 5 months of age[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	0.06	1	23
Male				
Body weight (g), PND 0	6.18 ± 0.57	6.12 ± 0.57 (−1)	6.3 ± 0.61 (+1.9)	6.08 ± 0.47 (−1.6)
Body weight (g), PND 90	444 ± 37	463 ± 31 (+4.3)	479 ± 28** (+7.9)	420 ± 21 (−5.4)
Body weight (g), PND 150	578 ± 38	545 ± 26 (−5.7)	578 ± 24 (0)	512 ± 35*** (−11.4)
Surface righting reflex (s), PND 3	4.39 ± 2.17	3.65 ± 1.85 (−16.9)	2.82 ± 1.63** (−35.8)	2.85 ± 1.42** (−35.1)
Surface righting reflex (s), PND 4	2.19 ± 0.85	2.33 ± 0.83 (+6.4)	1.81 ± 0.69* (−17.4)	1.89 ± 0.67* (−13.7)
Swimming time (s), PND 20	25.89 ± 20.32	27.42 ± 26.21 (+5.9)	31.76 ± 25.24* (+22.7)	13.98 ± 14.86* (−46)
Female				
Body weight (g), PND 0	6.17 ± 0.55	6.09 ± 0.48 (−1.3)	6.29 ± 0.62 (+1.9)	6.11 ± 0.39 (−1)
Body weight (g), PND 90 (g)	278 ± 15	271 ± 16 (−2.5)	280 ± 14 (+0.7)	264 ± 14 (−5)
Body weight (g), PND 150 (g)[c]	295 ± 13	285 ± 11 (−3.4)	291 ± 6 (−1.4)	269 ± 14*** (−8.8)
Surface righting reflex (s), PND 3	4.35 ± 1.99	3.65 ± 1.98 (−16.1)	2.80 ± 1.62** (−35.6)	2.88 ± 1.47** (−33.8)
Surface righting reflex (s), PND 4	2.2 ± 0.92	2.33 ± 0.79 (+5.9)	1.80 ± 0.58* (−18.2)	1.86 ± 0.66* (−15.5)
Swimming time (s), PND 20	25.32 ± 18.47	29.54 ± 25.31 (+16.7)	30.98 ± 27.38* (+22.4)	14.09 ± 14.22* (−44.4)

[a]Feng et al. (2006a).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 15/group except where noted.
[c]Group sizes were 6/dose for this endpoint in females.
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p \leq 0.001$), as reported by the study authors.

La = lanthanum; PND = postnatal day; SD = standard deviation.

Table B-14. Pyramidal Cells in the CA3 Region of the Hippocampus and Morris Water Maze Performance in Wistar Rat Pups Exposed to Lanthanum Chloride by Gavage from Birth to PND 20[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	**0.06**	**1**	**23**
Number of pyramidal cells in CA3 area of hippocampus				
n	4	4	4	4
Mean	325	299	265*	243**
SD	24	24	34	29
Length general path in Morris water maze (cm) at Session 4				
n	15	15	15	15
Mean	279	325	383*	493**
SD	112	157	112	202
Preference for target quadrant (percentage of time spent in target quadrant) at Session 4				
n	15	15	15	15
Mean	36	35	30*	28**
SD	5.8	5.0	6.7	5.8

[a]He et al. (2008)
[b]Data digitized from Figures 1B, 1C, and 6 of He et al. (2008); presented as mean ± SD (the reported SEM was converted to SD).
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

La = lanthanum; PND = postnatal day; SD = standard deviation (computed as SE × √ [n]); SE = standard error; SEM = standard error of the mean.

Table B-15. Representative Results, Morris Water Maze Performance in Wistar Rat Pups Exposed to Lanthanum Chloride by Drinking Water from Birth to PND 21[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	230.6 (maternal) 307.5 (pup)	461 (maternal) 615 (pup)	923 (maternal) 1,230 (pup)
Escape latency, D 1(s)	77.25 ± 9.25	75.13 ± 10.01 (−2.7)	80.5 ± 8.80 (+4.2)	82.88 ± 8.27 (+7.3)
Escape latency, D 2(s)	58.75 ± 11.16	69.50 ± 10.16* (+18)	75.25 ± 11.7* (+28)	81.38 ± 7.87* (+39)
Escape latency, D 3(s)	40.25 ± 9.05	53 ± 6.37* (+31.7)	68.13 ± 8.06* (+69.3)	73.63 ± 10.97* (+82.9)
Escape latency, D 4(s)	32.00 ± 6.23	42.25 ± 4.03* (+32)	54.50 ± 3.89* (+70.3)	57.88 ± 4.73* (+80.9)
Escape latency, D 5(s)	30.50 ± 5.07	34.00 ± 5.42 (+11.5)	37.13 ± 6.71 (+21.7)	39.25 ± 9.56 (+28.7)
Escape latency, D 12(s)	39.00 ± 9.74	59.13 ± 11.15[#] (+52)	68.13 ± 12.69[#] (+75)	84.50 ± 26.67[#] (+117)

[a]Yang et al. (2009).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 8/group.
*Statistically significantly different from same day control ($p < 0.05$), as reported by the study authors.
[#]Statistically significantly different from Day 5 result for same group ($p < 0.05$), as reported by the study authors.

La = lanthanum; PND = postnatal day; SD = standard deviation.

Table B-16. Hippocampal Synaptic Ultrastructure in Wistar Rats Exposed to Lanthanum Chloride via Lactation from Birth to PND 21 and via Drinking Water for 2 Months[a, b]

Endpoint	Dose (mg La/kg-d)			
	0	230.6 (maternal) 307.5 (pup)	461 (maternal) 615 (pup)	923 (maternal) 1,230 (pup)
Thickness of postsynaptic density (nm)	75.80 ± 6.1	58.96 ± 3.66* (−22.2)	47.83 ± 4.63* (−36.9)	39.28 ± 5.02* (−48.2)
Length of active zone (nm)	379.59 ± 19.43	308.36 ± 18.44* (−18.8)	242.45 ± 18.83* (−36)	212.41 ± 16.90* (−44)
Synaptic curvature (ratio of the synaptic arch length and chord length)	1.16 ± 0.06	1.12 ± 0.08* (−3.4)	1.11 ± 0.06* (−4.3)	1.07 ± 0.06* (−7.8)

[a]Liu et al. (2014).
[b]Data reported as mean ± SD (percent change compared with control); % change control = ([treatment mean − control mean] ÷ control mean) × 100; *n* = 50 synapses/group.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.

La = lanthanum; PND = postnatal day; SD = standard deviation.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with U.S. EPA's Benchmark Dose Software (BMDS, Version 2.5). For these data, all continuous models available within the software were fit using a default benchmark response (BMR) of 1 standard deviation (SD) relative risk. An adequate fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of the scaled residuals near the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model adequately fit the data (i.e., Test 3; p-value > 0.1), the final BMD results were estimated from a nonhomogeneous variance model. Otherwise, the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit (BMDL) was selected if the BMDLs estimated from different models varied greater than threefold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected.

BMD MODELING TO IDENTIFY POTENTIAL PODS FOR THE DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE DOSE

The endpoints subjected to BMD modeling from the study by He et al. (2008) include two measures of performance in the Morris water maze (length of pathway to platform and preference for the target quadrant) and the numbers of pyramidal cells in the CA3 region of the hippocampus. Table C-1 shows the dose-response data. Summaries of modeling approaches and results (see Tables C-2 to C-4 and Figures C-1 to C-3) for each data set follow.

Table C-1. Endpoints Subjected to BMD Modeling[a]				
	Dose (mg La/kg-d)			
Endpoint	**0**	**0.06**	**1**	**23**
Number of pyramidal cells in CA3 area of hippocampus				
n	4	4	4	4
Mean	325	299	265*	243**
SD	24	24	34	29
Length general path in Morris water maze (cm)				
n	15	15	15	15
Mean	279	325	383*	493**
SD	112	157	112	202
Preference for target quadrant (percentage of time spent in target quadrant)				
n	15	15	15	15
Mean	36	35	30*	28**
SD	5.8	5.0	6.7	5.8

[a]Data digitized from Figures 1B, 1C, and 6 of He et al. (2008).
*Statistically significantly different from control ($p \leq 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.

BMD = benchmark dose; La = lanthanum; SD = standard deviation.

Decreased Numbers of Hippocampal Pyramidal Cells

The procedure outlined above was applied to the data on numbers of pyramidal cells in the CA3 region of the hippocampus from the neurodevelopmental study by He et al. (2008) (see Table C-1). Table C-2 summarizes the BMD modeling results. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only the Exponential Models 4 and 5 and the Hill model provided adequate fit to the means. The BMDLs estimated from these models differed by less than threefold, so the model with the lowest BMDL (Hill model) was selected. The BMD and BMDL from this model were 0.083 and 0.016 mg La/kg-day, respectively. Figure C-1 shows the fit of the Hill model to the data; the textual BMD output for this model follows the figure.

Table C-2. BMD Model Predictions for Decreased Mean Pyramidal Cell Count in the CA3 Region of the Hippocampus in Male Rats Exposed to Lanthanum Chloride from GD 0 through 6 Months of Age[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	Scaled Residual: Dose Nearest the BMD[c]	AIC	BMD_{1SD} (mg La/kg-d)	$BMDL_{1SD}$ (mg La/kg-d)
Constant variance						
Exponential (Model 2)[d]	0.87	0.014	0.1008	132.57	12.314	7.193
Exponential (Model 3)[d]	0.87	0.014	0.1008	132.57	12.314	7.193
Exponential (Model 4)[d]	0.87	0.236	−0.8639	127.50	0.328	0.020
Exponential (Model 5)[d]	0.87	0.236	−0.8639	127.50	0.328	0.020
Hill[d, e]	**0.87**	**0.438**	**−0.341**	**126.70**	**0.083**	**0.016**
Linear[f]	0.87	0.014	0.0825	132.63	13.046	8.042
Polynomial (2-degree)[f]	0.87	0.014	0.0825	132.63	13.046	8.042
Polynomial (3-degree)[f]	0.87	0.014	0.0825	132.63	13.046	8.042
Power[d]	0.87	0.014	0.0825	132.63	13.046	8.042

[a]He et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also, the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, the Exponential Models 4 and 5 and the Hill model provided adequate fit to the means. BMDLs for models providing adequate fit were considered sufficiently close (differed by <two- to threefold), so the model with the lowest AIC was selected (Hill).
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response; GD = gestation day; La = lanthanum; SD = standard deviation.

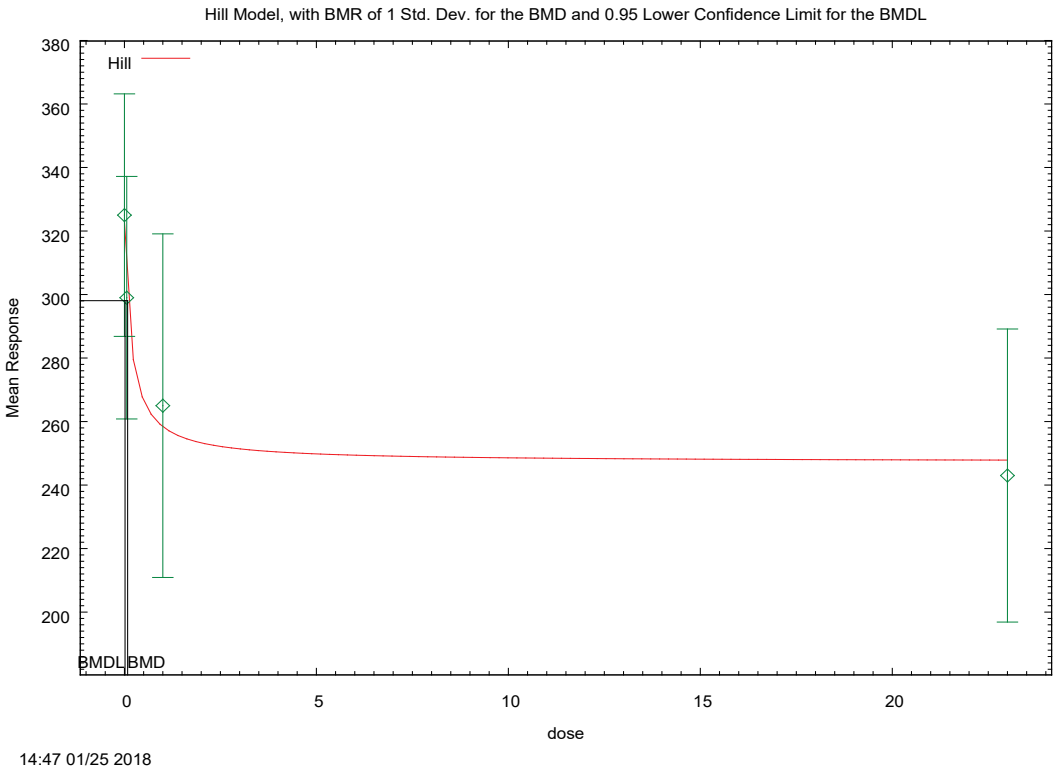

Figure C-1. Fit of the Hill Model to Data on Reduced Numbers of Pyramidal Cells in Rats Exposed to Lanthanum Chloride from GD 0 to 6 Months of Age (He et al., 2008)

Text Output for Figure C-1:

```
 ================================================================
        Hill Model. (Version: 2.17;  Date: 01/28/2013)
        Input Data File:
C:/Users/jzhao/BMDS2601/Data/hil_UntitledData1_Hil-ConstantVariance-BMR1Std-Restrict.(
d)
        Gnuplot Plotting File:
C:/Users/jzhao/BMDS2601/Data/hil_UntitledData1_Hil-ConstantVariance-BMR1Std-Restrict.p
lt
                                                Thu Jan 25 14:47:33 2018
 ================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
```

Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	787.25	
rho =	0	Specified
intercept =	325	
v =	-82	
n =	0.858778	
k =	0.474706	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	-1.8e-007	2.9e-007	-1.1e-006
intercept	-1.8e-007	1	-0.63	-0.67
v	2.9e-007	-0.63	1	0.073
k	-1.1e-006	-0.67	0.073	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	613.065	216.751	188.24	1037.89
intercept	322.825	13.6418	296.088	349.562
v	-75.6737			
			15.1317	-105.331	-46.016
n	1	NA		
k	0.171655	0.241307	-0.301297	0.644607

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	325	323	24	24.8	0.176
0.06	4	299	303	24	24.8	-0.341

1	4	265	258	34	24.8	0.546
23	4	243	248	29	24.8	-0.381

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-59.046910	5	128.093821
A2	-58.697599	8	133.395199
A3	-59.046910	5	128.093821
fitted	-59.347763	4	126.695526
R	-66.903383	2	137.806765

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	16.4116	6	0.01171
Test 2	0.698622	3	0.8735
Test 3	0.698622	3	0.8735
Test 4	0.601705	1	0.4379

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

```
        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =      0.0834788

            BMDL =     0.0158129
```

Increased Length of General Path in Morris Water Maze

The procedure outlined above was applied to the data on increased length of general path in Morris water maze from the neurodevelopmental study by He et al. (2008) (see Table C-1). Table C-3 summarizes the BMD modeling results. The constant variance model did not provide adequate fit to the variance data; however, variance was modeled adequately using the nonconstant variance model in BMDS. With the nonconstant variance model applied, only the Exponential models (all) and the Power model provided adequate fit to the means. While the Hill model provided an apparent fit to the means, this model did not return a BMDL estimate. The BMDLs for models providing adequate fit varied by greater than threefold, so the model with the lowest BMDL (Exponential Models 4 and 5) was selected. The BMD and BMDL from this model were 2.46 and 0.70 mg La/kg-day, respectively. Figure C-2 shows the fit of the Exponential Model 4 to the data; the textual BMD output for this model follows the figure.

Table C-3. BMD Model Predictions for Increased General Path Distance in Morris Water Maze in Male Rats Exposed to Lanthanum Chloride from GD 0 through 6 Months of Age[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	Scaled Residual: Dose Nearest the BMD[c]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance						
Exponential (Model 2)[d]	0.055	0.1895	−0.038	666.82	20.88	15.43
Exponential (Model 3)[d]	0.055	0.1895	−0.038	666.82	20.88	15.43
Exponential (Model 4)[d]	0.055	0.4598	−0.057	666.04	2.32	0.73
Exponential (Model 5)[d]	0.055	0.4598	−0.057	666.04	2.32	0.73
Hill[d]	0.055	0.4838	−0.095	665.99	3.06	0.33
Linear[e]	0.055	0.1985	−0.056	666.73	20.26	13.84
Polynomial (2-degree)[e]	0.055	0.1985	−0.056	666.73	20.26	13.84
Polynomial (3-degree)[e]	0.055	0.1985	−0.056	666.73	20.26	13.84
Power[e]	0.055	0.1985	−0.056	666.73	20.26	13.84
Nonconstant variance						
Exponential (Model 2)[d]	0.235	0.1327	−0.064	664.84	18.38	12.63
Exponential (Model 3)[d]	0.235	0.1327	−0.064	664.84	18.38	12.63
Exponential (Model 4)[e, f]	**0.235**	**0.1511**	**0.382**	**664.87**	**2.46**	**0.70**
Exponential (Model 5)[d]	0.235	0.1511	0.382	664.87	2.46	0.70
Hill[d]	0.235	0.1567	0.336	664.81	2.89	NA
Linear[e]	0.235	0.1397	−0.091	664.74	17.30	10.76
Polynomial (2-degree)[e]	0.235	0.1397	−0.091	664.74	17.30	10.76

Table C-3. BMD Model Predictions for Increased General Path Distance in Morris Water Maze in Male Rats Exposed to Lanthanum Chloride from GD 0 through 6 Months of Age[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	Scaled Residual: Dose Nearest the BMD[c]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Polynomial (3-degree)[e]	0.235	0.1397	−0.091	664.74	17.30	10.76
Power[d]	0.235	0.1397	−0.091	664.74	17.30	10.76

[a]He et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also, the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance model did not fit variance data, but the model variance model did. With nonhomogeneous variance model applied, the exponential and power models provided adequate fit to the means. BMDLs for models providing adequate fit were not sufficiently close (differed by >two- to threefold), so the model with the lowest BMDL was selected (Exponential Model 4; Exponential Model 5 converged onto Model 4).

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; GD = gestation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested) or there is no scaled residual at the dose below the BMD because the BMD value is the lowest dose tested (0 mg/kg-d-control); SD = standard deviation.

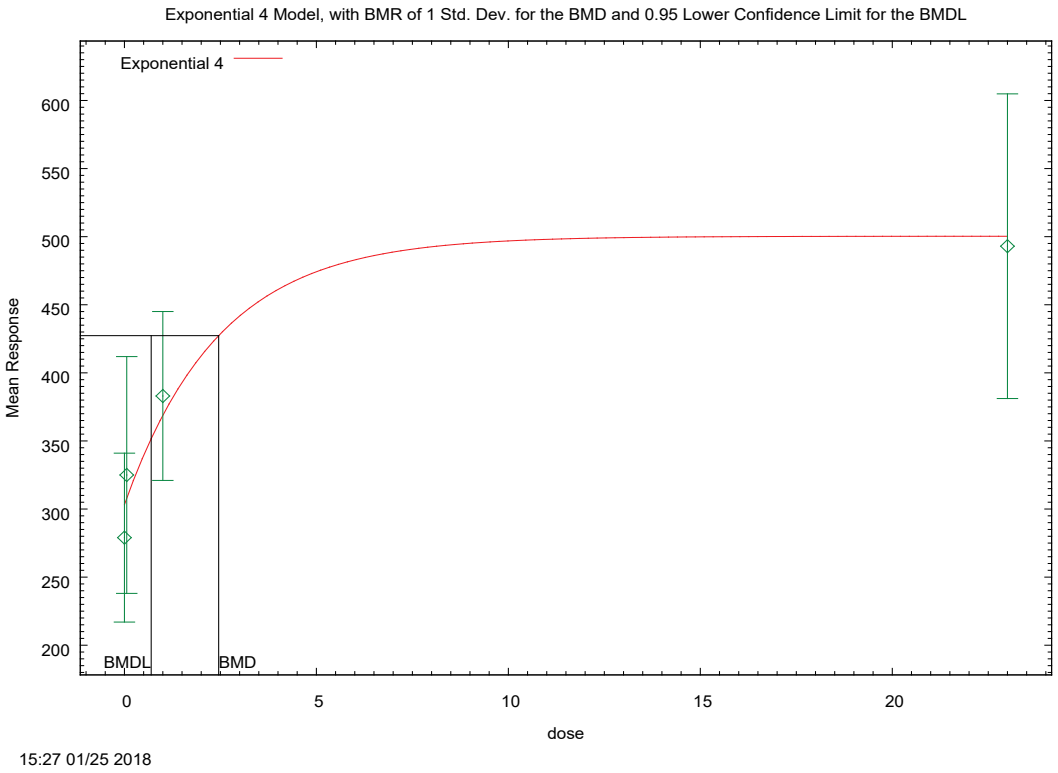

Figure C-2. Fit of the Exponential Model 4 to Data on Length of General Path in Morris Water Maze in Male Rats Exposed to Lanthanum Chloride from GD 0 to 6 Months of Age (He et al., 2008)

Text Output for Figure C-2:

```
 ================================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File:
C:/Users/jzhao/BMDS2601/Data/exp_UntitledData2_Exp-ModelVariance-BMR1Std-Up.(d)
        Gnuplot Plotting File:
                                                 Thu Jan 25 15:27:31 2018
 ================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4	
lnalpha	0.209421	
rho	1.64514	
a	265.05	
b	0.102201	
c	1.95303	
d	1	Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	0.91838	5.61445
rho	1.52673	0.951704
a	303.181	24.6196
b	0.404591	0.332096
c	1.65021	0.202799

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	15	279	112
0.06	15	325	157
1	15	383	112
23	15	493	202

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	303.2	124.1	-0.7545
0.06	307.9	125.6	0.527
1	368.8	144.1	0.3822
23	500.3	181.9	-0.1553

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)

```
           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-328.7481	5	667.4962
A2	-324.9529	8	665.9058
A3	-326.4027	6	664.8055
R	-336.6879	2	677.3759
4	-327.4334	5	664.8667

Additive constant for all log-likelihoods = -55.14. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	23.47	6	0.0006534
Test 2	7.59	3	0.05528
Test 3	2.9	2	0.2346
Test 6a	2.061	1	0.1511

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is less than .1. A non-homogeneous variance model appears to be appropriate.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

```
        Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =      2.45522

            BMDL =     0.697328
```

Decreased Preference for Target Quadrant in Morris Water Maze

The procedure outlined above was applied to the data on decreased preference for target quadrant in the Morris water maze from the neurodevelopmental study by He et al. (2008) (see Table C-1). Table C-4 summarizes the BMD modeling results. The constant variance model provided adequate fit to the variance data. With the constant variance model applied, only Exponential Models 4 and 5 provided adequate fit to the means. The BMDLs from these models only differed by less than twofold, which would typically lead to selection of the model with the lowest AIC. However, the AICs (as well as scaled residuals) were identical for both models. Exponential Model 4 was selected because it is more parsimonious (i.e., has fewer parameters). The BMD and BMDL from this model were 0.93 and 0.11 mg La/kg-day, respectively. Figure C-3 shows the fit of the Exponential Model 4 to the data; the textual BMD output for this model follows the figure.

Table C-4. BMD Model Predictions for Target Quadrant Preference in Morris Water Maze in Male Rats Exposed to Lanthanum Chloride from GD 0 through 6 Months of Age[a]

Model	Variance *p*-Value[b]	Mean *p*-Value[b]	Scaled Residual: Dose nearest BMD[c]	AIC	BMD_{1SD} (mg/kg-d)	$BMDL_{1SD}$ (mg/kg-d)
Constant variance						
Exponential (Model 2)[d]	0.7344	0.01671	0.116	282.14	23.20	14.39
Exponential (Model 3)[d]	0.7344	0.01671	0.116	282.14	23.20	14.39
Exponential (Model 4)[d, e]	**0.7344**	**0.8539**	**0.030**	**275.99**	**0.93**	**0.11**
Exponential (Model 5)[d]	0.7344	0.8539	0.030	275.99	0.93	0.06
Hill[d]	0.7344	NA	0.000	277.96	0.82	0.07
Linear[f]	0.7344	0.01613	0.097	282.21	23.39	15.30
Polynomial (2-degree)[f]	0.7344	0.01613	0.097	282.21	23.39	15.30
Polynomial (3-degree)[f]	0.7344	0.01613	0.097	282.21	23.39	15.30
Power[d]	0.7344	0.01613	0.097	282.21	23.39	15.30

[a]He et al. (2008).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model provided adequate fit to variance data. With constant variance applied, only Exponential Models 4 and 5 provided adequate fit to the means. The BMDLs for these two models are sufficiently close (differ by <two- to threefold), so typically the lowest AIC would be selected. The AICs and goodness-of-fit statistics are identical for the Exponential 4 and 5 models. Exponential Model 4 was selected because it is more parsimonious (fewer parameters).
[f]Coefficients restricted to be negative.

AIC = Akaike's information criterion; BMD = benchmark dose; BMDL = benchmark dose lower confidence limit; GD = gestation day; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation.

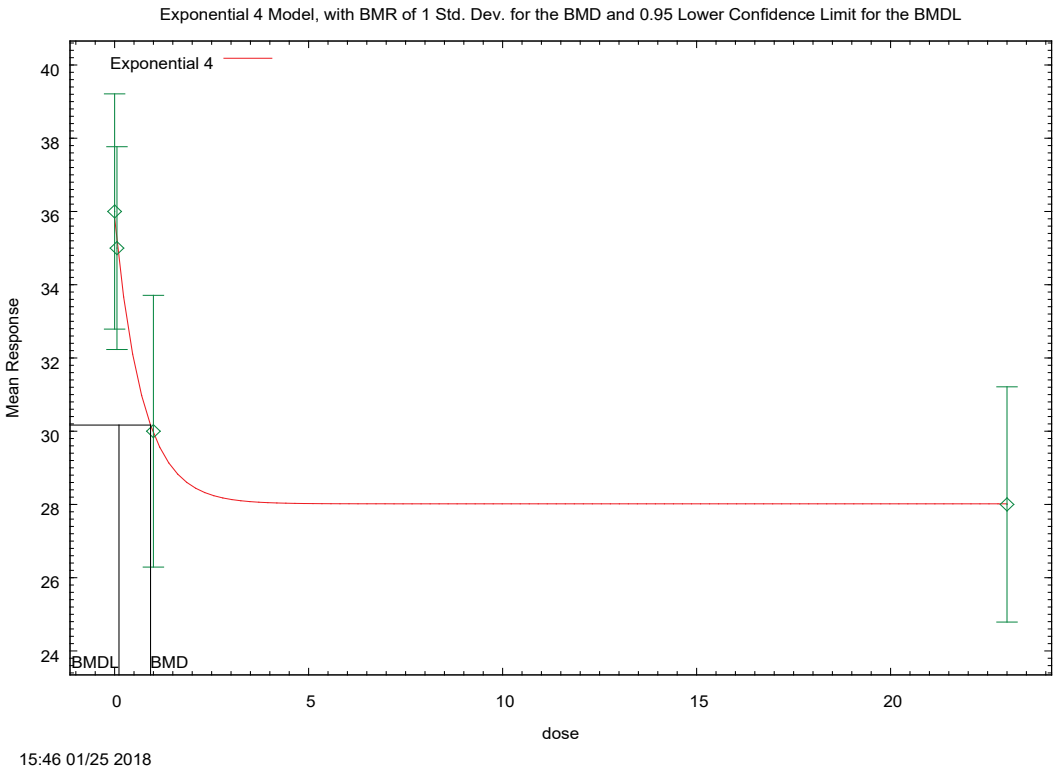

Figure C-3. Fit of the Exponential Model 4 to Data on Decreased Preference for Target Quadrant in Morris Water Maze in Male Rats Exposed to Lanthanum Chloride from GD 0 to 6 Months of Age (He et al., 2008)

Text Output for Figure C-3:

```
 ================================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File:
C:/Users/jzhao/BMDS2601/Data/exp_UntitledData3_Exp-ConstantVariance-BMR1Std-Down.(d)
        Gnuplot Plotting File:
                                                  Thu Jan 25 15:46:57 2018
 ================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.
```

```
Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact
```

Initial Parameter Values

Variable	Model 4	
lnalpha	3.46593	
rho	0	Specified
a	37.8	
b	0.0944057	
c	0.705467	
d	1	Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	3.4665	5.84684
a	35.8268	1.12
b	1.39365	0.978065
c	0.782024	0.0464124

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	15	36	5.8
0.06	15	35	5
1	15	30	6.7
23	15	28	5.8

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	35.83	5.659	0.1185
0.06	35.2	5.659	-0.1371
1	29.96	5.659	0.03049
23	28.02	5.659	-0.01192

```
Other models for which likelihoods are calculated:

  Model A1:        Yij = Mu(i) + e(ij)
```

```
           Var{e(ij)} = Sigma^2

  Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
           Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-133.978	5	277.956
A2	-133.3391	8	282.6783
A3	-133.978	5	277.956
R	-142.9709	2	289.9419
4	-133.995	4	275.99

Additive constant for all log-likelihoods = -55.14. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	19.26	6	0.003741
Test 2	1.278	3	0.7344
Test 3	1.278	3	0.7344
Test 6a	0.03393	1	0.8539

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

```
       Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

             BMD =     0.925403

            BMDL =     0.112065
```

APPENDIX D. 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.

Abramczuk, JW. (1985). The effects of lanthanum chloride on pregnancy in mice and on preimplantation mouse embryos in vitro. Toxicology 34: 315-320. http://dx.doi.org/10.1016/0300-483X(85)90142-8.

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.

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.

Briner, W; Rycek, RF; Moellenberndt, A; Dannull, K. (2000). Neurodevelopmental effects of lanthanum in mice. Neurotoxicol Teratol 22: 573-581.

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.

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 chemical database. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from https://oehha.ca.gov/chemicals

Che, Y; Cui, Y; Jiang, X. (2009). Effects of lanthanum chloride administration in prenatal stage on one-trial passive avoidance learning in chicks. Biol Trace Elem Res 127: 37-44. http://dx.doi.org/10.1007/s12011-008-8225-5.

Che, Y; Xing, R; Zhu, Y; Cui, Y; Jiang, X. (2011). Effects of lanthanum chloride administration on detouring learning in chicks. Biol Trace Elem Res 143: 274-280. http://dx.doi.org/10.1007/s12011-010-8860-5.

Chen, D; Liu, Y; Chen, AJ; Nie, YX. (2003). Experimental study of subchronic toxicity of lanthanum nitrate on liver in rats. Nonlinearity Biol Toxicol Med 1: 469-480. http://dx.doi.org/10.1080/15401420390271074.

Cochran, KW; Doull, J; Mazur, M; Dubois, KP. (1950). Acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum and yttrium. Arch Ind Hyg Occup Med 1: 637-650.

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

Cuddihy, RG; Boecker, BB. (1970). Kinetics of lanthanum retention and tissue distribution in the Beagle dog following administration of 140 LaCl 3 by inhalation, gavage and injection. Health Phys 19: 419-426. http://dx.doi.org/10.1097/00004032-197009000-00005.

Damment, SJ; Cox, AG; Secker, R. (2009). Dietary administration in rodent studies distorts the tissue deposition profile of lanthanum carbonate; brain deposition is a contamination artefact. Toxicol Lett 188: 223-229. http://dx.doi.org/10.1016/j.toxlet.2009.03.020.

Damment, SJ; Pennick, M. (2007). Systemic lanthanum is excreted in the bile of rats. Toxicol Lett 171: 69-77. http://dx.doi.org/10.1016/j.toxlet.2007.04.005.

De, SK; Sharma, A. (1981). Mutachromosomic effects of lanthanum chloride on mammalian bone marrow. Curr Sci 50: 189-190.

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). (2016). Table 3: Protective Action Criteria (PAC) Rev. 28 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. February 2016. Washington, DC. https://sp.eota.energy.gov/pac/teel/Revision_28A_Table3.pdf.

Dubois, KP. (1956). Chemical toxicity of salts of lanthanum, yttrium and some other rare metals to animals. In Rare earths in biochemical and medical research (pp. 91-101). (Niosh/00134840). Oak Ridge, TN: Oak Ridge Institute of Nuclear Studies.

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.

Fang, HQ; Yu, Z; Zhi, Y; Fang, J; Li, CX; Wang, YM; Peng, SQ; Jia, XD. (2018). Subchronic oral toxicity evaluation of lanthanum: A 90-day, repeated dose study in rats. Biomed Environ Sci 31: 363-375. http://dx.doi.org/10.3967/bes2018.047.

Fei, M; Li, N; Ze, Y; Liu, J; Wang, S; Gong, X; Duan, Y; Zhao, X; Wang, H; Hong, F. (2011). The mechanism of liver injury in mice caused by lanthanoids. Biol Trace Elem Res 140: 317-329. http://dx.doi.org/10.1007/s12011-010-8698-x.

Feng, L; Xiao, H; He, X; Li, Z; Li, F; Liu, N; Chai, Z; Zhao, Y; Zhang, Z. (2006a). Long-term effects of lanthanum intake on the neurobehavioral development of the rat. Neurotoxicol Teratol 28: 119-124. http://dx.doi.org/10.1016/j.ntt.2005.10.007.

Feng, L; Xiao, H; He, X; Li, Z; Li, F; Liu, N; Zhao, Y; Huang, Y; Zhang, Z; Chai, Z. (2006b). Neurotoxicological consequence of long-term exposure to lanthanum. Toxicol Lett 165: 112-120. http://dx.doi.org/10.1016/j.toxlet.2006.02.003.

Floren, C; Tekaya, L; Escaig, F; Labejof, L; Mouthon, G; Galle, P. (2001). Analytical microscopy observations of rat enterocytes after oral administration of soluble salts of lanthanides, actinides and elements of group III-A of the periodic chart. Cell Mol Biol (Noisy-le-grand) 47: 419-425.

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.

Hao, S; Yu, F; Yan, A; Zhang, Y; Han, J; Jiang, X. (2012). In utero and lactational lanthanum exposure induces olfactory dysfunction associated with downregulation of βIII-tubulin and olfactory marker protein in young rats. Biol Trace Elem Res 148: 383-391. http://dx.doi.org/10.1007/s12011-012-9386-9.

Harris, RA; Iwamoto, ET; Loh, HH; Way, EL. (1975). Site dependent analgesia after microinjection of morphine or lanthanum in rat brain. Proc West Pharmacol Soc 18: 275-278.

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

He, ML; Wang, YZ; Xu, ZR; Chen, ML; Rambeck, WA. (2003). Effect of dietary rare earth elements on growth performance and blood parameters of rats. J Anim Physiol Anim Nutr 87: 229-235. http://dx.doi.org/10.1046/j.1439-0396.2003.00432.x.

He, X; Zhang, Z; Zhang, H; Zhao, Y; Chai, Z. (2008). Neurotoxicological evaluation of long-term lanthanum chloride exposure in rats. Toxicol Sci 103: 354-361. http://dx.doi.org/10.1093/toxsci/kfn046.

Hong, J; Pan, X; Zhao, X; Yu, X; Sang, X; Sheng, L; Wang, X; Gui, S; Sun, Q; Wang, L; Hong, F. (2015). Molecular mechanism of oxidative damage of lung in mice following exposure to lanthanum chloride. Environ Toxicol 30: 357-365. http://dx.doi.org/10.1002/tox.21913.

Hu, X; Yang, J; Sun, Y; Gao, X; Zhang, L; Li, Y; Yu, M; Liu, S; Lu, X; Jin, C; Wu, S; Cai, Y. (2018). Lanthanum chloride impairs memory in rats by disturbing the glutamate-glutamine cycle and over-activating NMDA receptors. Food Chem Toxicol 113: 1-13. http://dx.doi.org/10.1016/j.fct.2018.01.023.

Huang, J; Zhang, TL; Xu, SJ; Li, RC; Wang, K; Zhang, J; Xie, YN. (2006). Effects of lanthanum on composition, crystal size, and lattice structure of femur bone mineral of Wistar rats. Calcif Tissue Int 78: 241-247. http://dx.doi.org/10.1007/s00223-005-0294-2.

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/

Jiang, C; Shang, J; Li, Z; Qin, A; Ouyang, Z; Qu, X; Li, H; Tian, B; Wang, W; Wu, C; Wang, J; Dai, M. (2016). Lanthanum chloride attenuates osteoclast formation and function via the downregulation of Rankl-induced Nf-κb and Nfatc1 activities. J Cell Physiol 231: 142-151. http://dx.doi.org/10.1002/jcp.25065.

Jin, C; Gao, L; Li, Y; Wu, S; Lu, X; Yang, J; Cai, Y. (2017). Lanthanum damages learning and memory and suppresses astrocyte-neuron lactate shuttle in rat hippocampus. Exp Brain Res 235: 3817-3832. http://dx.doi.org/10.1007/s00221-017-5102-5.

Kádas, I; Jobst, K. (1973). Liver damage induced by lanthanum trichloride. Acta Morphol Acad Sci Hung 21: 27-37.

Kádas, I; Lapis, K; Jobst, K. (1974). Electron microscopic studies of liver changes induced by lanthanum trichloride. Acta Morphol Acad Sci Hung 22: 343-357.

Kádas, I; Tanka, D; Keller, M; Jobst, K. (1973). Enzyme-histochemical and biochemical aspects of liver damage caused by lanthanum trichloride [Abstract]. Acta Morphol Acad Sci Hung Suppl 14: 77.

Kanematsu, N; Hara, M; Kada, T. (1980). REC assay and mutagenicity studies on metal compounds. Mutat Res 77: 109-116. http://dx.doi.org/10.1016/0165-1218(80)90127-5.

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

Kubinski, H; Gutzke, GE; Kubinski, ZO. (1981). DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. Mutat Res 89: 95-136. http://dx.doi.org/10.1016/0165-1218(81)90118-X.

Kuzmin, AV; Zwartau, EE. (1996). Intracerebroventricular La3+ but not Gd3+ inhibits cocaine-induced motor activation in rats. Eur Neuropsychopharmacol 6: 183-185. http://dx.doi.org/10.1016/0924-977X(96)00017-X.

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). Lanthanum. In RJ Lewis, Sr.; GG Hawley (Eds.), Hawley's condensed chemical dictionary (15th ed., pp. 738-739). Hoboken, NJ: John Wiley & Sons. http://dx.doi.org/10.1002/9780470114735.hawley09602.

Li, N; Wang, S; Liu, J; Ma, L; Duan, Y; Hong, F. (2010). The oxidative damage in lung of mice caused by lanthanoide. Biol Trace Elem Res 134: 68-78. http://dx.doi.org/10.1007/s12011-009-8448-0.

Liapi, C; Zarros, A; Theocharis, S; Al-Humadi, H; Anifantaki, F; Gkrouzman, E; Mellios, Z; Skandali, N; Tsakiris, S. (2009). The neuroprotective role of L-cysteine towards the effects of short-term exposure to lanthanum on the adult rat brain antioxidant status and the activities of acetylcholinesterase, (Na+,K+)- and Mg2+-ATPase. Biometals 22: 329-335. http://dx.doi.org/10.1007/s10534-008-9169-0.

Liu, D; Zhang, J; Wang, G; Liu, X; Wang, S; Yang, M. (2012). The dual-effects of LaCl on the proliferation, osteogenic differentiation, and mineralization of MC3T3-E1 cells. Biol Trace Elem Res 150: 433-440. http://dx.doi.org/10.1007/s12011-012-9486-6.

Liu, H; Yang, J; Liu, Q; Jin, C; Wu, S; Lu, X; Zheng, L; Xi, Q; Cai, Y. (2014). Lanthanum chloride impairs spatial memory through ERK/MSK1 signaling pathway of hippocampus in rats. Neurochem Res 39: 2479-2491. http://dx.doi.org/10.1007/s11064-014-1452-6.

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.

Nagano, M; Shimada, H; Funakoshi, T; Yasutake, A. (2000). Increase of calcium concentration in the testes of mice treated with rare earth metals. J Health Sci 46: 314-316.

Nagy, I; Kádas, I; Jobst, K. (1976). Lanthanum Trichloride induced blood coagulation defect and liver injury. Haematologia (Budap) 10: 353-359.

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.

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.

Nishioka, H. (1975). Mutagenic activities of metal compounds in bacteria. Mutat Res 31: 185-189. http://dx.doi.org/10.1016/0165-1161(75)90088-6.

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.

Ogawa, Y. (1992). Studies on the biological effects of lanthanum: Effects of repeated oral administration tests in rats. Jpn J Toxicol Environ Health 38: 545-553.

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.

Rabinowitz, JL; Fernandez-Gavarron, F; Brand, JG. (1988). Tissue uptake and intracellular distribution of 140-lanthanum after oral intake by the rat. J Toxicol Environ Health 24: 229-235. http://dx.doi.org/10.1080/15287398809531156.

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.

Summers, MJ; Crowe, SF; Ng, KT. (1996). Administration of lanthanum chloride following a reminder induces a transient loss of memory retrieval in day-old chicks. Brain Res Cogn Brain Res 4: 109-119.

Suzuki, KT; Kobayashi, E; Ito, Y; Ozawa, H; Suzuki, E. (1992). Localization and health effects of lanthanum chloride instilled intratracheally into rats. Toxicology 76: 141-152.

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). (2011). 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). (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.

Wadkins, T; Benz, J; Briner, W. (1998). The effect of lanthanum administration during neural tube formation on the emergence of swimming behavior. Paper presented at 5th International Symposium on Metal Ions in Biology and Medicine, May 8-10, 1998, Neuherberg/Munich, Germany.

Wang, X; Yuan, L; Huang, J; Zhang, TL; Wang, K. (2008). Lanthanum enhances in vitro osteoblast differentiation via pertussis toxin-sensitive gi protein and ERK signaling pathway. J Cell Biochem 105: 1307-1315. http://dx.doi.org/10.1002/jcb.21932.

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.

Yang, J; Liu, Q; Wu, S; Xi, Q; Cai, Y. (2013). Effects of lanthanum chloride on glutamate level, intracellular calcium concentration and caspases expression in the rat hippocampus. Biometals 26: 43-59. http://dx.doi.org/10.1007/s10534-012-9593-z.

Yang, J; Liu, Q; Zhang, L; Wu, S; Qi, M; Lu, S; Xi, Q; Cai, Y. (2009). Lanthanum chloride impairs memory, decreases pCaMK IV, pMAPK and pCREB expression of hippocampus in rats. Toxicol Lett 190: 208-214. http://dx.doi.org/10.1016/j.toxlet.2009.07.016.

Yongxing, W; Xiaorong, W; Zichun, H. (2000). Genotoxicity of lanthanum (III) and gadolinium (III) in human peripheral blood lymphocytes. Bull Environ Contam Toxicol 64: 611-616.

Zarros, A; Byrne, AM; Boomkamp, SD; Tsakiris, S; Baillie, GS. (2013). Lanthanum-induced neurotoxicity: solving the riddle of its involvement in cognitive impairment? [Letter]. Arch Toxicol 87: 2031-2035. http://dx.doi.org/10.1007/s00204-013-1112-7.

Zeiger, E; Anderson, B; Haworth, S; Lawlor, T; Mortelmans, K. (1992). Salmonella mutagenicity tests: V Results from the testing of 311 chemicals. Environ Mol Mutagen 19: 2-141. http://dx.doi.org/10.1002/em.2850190603.

Zhang, D; Zhang, J; Chen, Y; Yang, M; Yao, X. (2007). Effects of lanthanum and gadolinium on proliferation and differentiation of primary osteoblasts. Prog Nat Sci 17: 618-623. http://dx.doi.org/10.1080/10020070708541044.

Zhang, L; Yang, J; Jin, C; Wu, S; Lu, X; Hu, X; Sun, Y; Cai, Y. (2017). The effect of nuclear factor erythroid 2-related factor/antioxidant response element signalling pathway in the lanthanum chloride-induced impairment of learning and memory in rats. J Neurochem 140: 463-475. http://dx.doi.org/10.1111/jnc.13895.

Zhao, H; Cheng, Z; Hu, R; Chen, J; Hong, M; Zhou, M; Gong, X; Wang, L; Hong, F. (2011). Oxidative injury in the brain of mice caused by lanthanid. Biol Trace Elem Res 142: 174-189. http://dx.doi.org/10.1007/s12011-010-8759-1.

Zhao, H; Hong, J; Yu, X; Zhao, X; Sheng, L; Ze, Y; Sang, X; Gui, S; Sun, Q; Wang, L; Hong, F. (2013). Oxidative stress in the kidney injury of mice following exposure to lanthanides trichloride. Chemosphere 93: 875-884. http://dx.doi.org/10.1016/j.chemosphere.2013.05.034.

Zheng, L; Yang, J; Liu, Q; Yu, F; Wu, S; Jin, C; Lu, X; Zhang, L; Du, Y; Xi, Q; Cai, Y. (2013). Lanthanum chloride impairs spatial learning and memory and downregulates NF-κB signalling pathway in rats. Arch Toxicol 87: 2105-2117. http://dx.doi.org/10.1007/s00204-013-1076-7.