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Provisional Peer-Reviewed Toxicity Values for

Stable (Nonradioactive) Gadolinium (CASRN 7440-54-2) and Soluble Salts

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

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COMMONLY USED ABBREVIATIONS AND ACRONYMS[1]

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

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

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR STABLE (NONRADIOACTIVE) GADOLINIUM (CASRN 7440-54-2) 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.

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 EPA Office of Research and Development's (ORD's) NCEA, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Gadolinium, CASRN 7440-54-2, is a metallic element of the lanthanide series with an atomic number of 64. It is used in neutron shielding, in synthetic garnets to filter microwaves, as a phosphor activator, as a catalyst, and as a scavenger for oxygen in titanium production (Lewis and Hawley, 2007). Various gadolinium 3^+ complexes are used as magnetic resonance imaging (MRI) contrast agents (Caravan et al., 1999). Gadolinium is listed on U.S. EPA's Toxic Substances Control Act's public inventory (U.S. EPA, 2018b); however, it is not registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program (ECHA, 2018).

Gadolinium occurs naturally in the earth's crust at a concentration of approximately 6.2 ppm (Bunzli, 2013). Lanthanides, such as gadolinium, typically occur in compounds as trivalent cations in insoluble carbonates, oxides, phosphates, and silicates (USGS, 2016). Gadolinium is found in several minerals including gadolinite and two commercially important minerals, monazite and bastnäsite (Haynes, 2014). Monazite is digested using caustic soda to obtain the lanthanides as hydroxides, which are then treated with hydrochloric or nitric acid to remove thorium and other elements, and finally treated to recover the individual lanthanides. A similar process can be used for bastnäsite (Bunzli, 2013).

Gadolinium is a malleable, ductile, silvery-white metal (Haynes, 2014). Gadolinium metal is insoluble in water, but soluble in dilute acid (Lewis and Hawley, 2007). It exhibits a high degree of magnetism and has superconductive properties. It is combustible and burns in air to form the oxide (Lewis and Hawley, 2007). Like other lanthanides, gadolinium 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 PPRTV assessment pertains exclusively to gadolinium and soluble salts. Soluble gadolinium salts (such as gadolinium chloride and gadolinium nitrate), once dissolved and administered, would rapidly form gadolinium 3^+ ions with bound water molecules in aqueous solution and biological systems. The solubility of gadolinium 3^+ in aqueous solution is pH dependent. At pH below approximately 6, the gadolinium 3^+ ion is bound to water molecules as the soluble aqua ion ($Gd[H_2O]_8^{3+}$). This would be the predominant gadolinium species found in the stomach (pH 1−2). Above pH 6, as would be found in the small intestines and blood, gadolinium will begin to precipitate out of solution as the bound water molecules are converted to hydroxide ions ($Gd[OH]_3[H_2O]_5$) (Sherry et al., 2009; Evans, 1990). Some lanthanide 3^+ ions may also bind to other oxygen donor molecules such as carboxylic acids (proteins) and phosphates (nucleic acids), suggesting that gadolinium may possess the ability to modify protein/enzyme function in biological systems (Evans, 1990). Table 1 summarizes the physicochemical properties of gadolinium and soluble salts.

Table 1. Physicochemical Properties of Gadolinium and Soluble Salts[a]

Property (unit)	Gadolinium	Gadolinium Chloride	Gadolinium Nitrate[b]
CASRN	7440-54-2	10138-52-0	10168-81-7
Formula	Gd	$GdCl_3$	$Gd(NO_3)_3$
Physical state	Solid	Solid	Solid
Boiling point (°C)	3,273[a]	NA	NA
Melting point (°C)	1,313[a]	602[a]	92 (decomposes)[a]
Density (g/cm^3 at 25°C)	7.90[a]	4.52[a]	2.41[a]
Vapor pressure (mm Hg at 25°C)	NA	NA	NA
pH at which precipitation starts (in solution of 0.1 M $Gd[NO_3]_3$)	6.58 (ion)[c]	NA	NA
Solubility in water (mg/L at 25°C)	Insoluble[d]	Soluble[a]	1.9×10^{6}, [a]
Formula weight (g/mol)	157.25[a]	263.61[a]	433.34[a]
Flash point (°C)	NA	NV	NV

[a]Haynes (2014).
[b]Note: Data for the pentahydrate (CASRN 52788-53-1) are shown.
[c]Bunzli (2013).
[d]Lewis and Hawley (2007).

NA = not applicable; NV = not available.

Gadolinium chloride ($GdCl_3$), CASRN 10138-52-0, is a hygroscopic, white monoclinic crystalline solid that is soluble in water (Haynes, 2014). It is produced by crystallization of aqueous chloride solutions (Bunzli, 2013). It is used as a gadolinium sponge metal (a production source of gadolinium metal) by contact with a reducing metal vapor (Lewis and Hawley, 2007). Gadolinium chloride is also found as the hexahydrate ($GdCl_3 \cdot 6H_2O$), CASRN 13450-84-5.

Gadolinium nitrate ($Gd[NO_3]_3$), CASRN 10168-81-7, exists as hygroscopic crystals that are soluble in water (Haynes, 2014). Two hydrated forms are known, gadolinium nitrate pentahydrate, CASRN 52788-53-1, and gadolinium nitrate hexahydrate, CASRN 19598-90-4.

A summary of available toxicity values for gadolinium and its salts from EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Gadolinium and Soluble Salts

Source (parameter)[a, b]		Value (applicability)	Notes	Reference
Noncancer				
IRIS		NV	NA	U.S. EPA (2018a)
HEAST		NV	NA	U.S. EPA (2011a)
DWSHA		NV	NA	U.S. EPA (2012)
ATSDR		NV	NA	ATSDR (2017)
IPCS		NV	NA	IPCS (2018); WHO (2018)
CalEPA		NV	NA	CalEPA (2014); CalEPA (2017); CalEPA (2018)
OSHA		NV	NA	OSHA (2006); OSHA (2011)
NIOSH		NV	NA	NIOSH (2016)
ACGIH		NV	NA	ACGIH (2017)
DOE (PAC)	Gadolinium	PAC-1: 30 mg/m^3; PAC-2: 330 mg/m^3; PAC-3: 2,000 mg/m^3	PAC-3 and PAC-2 based on adjustments to 1-hr TEELs; PAC-1 based on ACGIH TLV-TWA for insoluble or poorly soluble particles not otherwise specified.	DOE (2016) Documentation of the basis for TEEL values was not located.
	$GdCl_3$ $6H_2O$	PAC-1: 2.2 mg/m^3; PAC-2: 24 mg/m^3; PAC-3: 140 mg/m^3	PAC-1 and PAC-2 based on adjustments to 1-hr TEELs; PAC-3 based on mouse i.p. LD_{50}.	
	$Gd(NO_3)_3$, solid	PAC-1: 11 mg/m^3; PAC-2: 130 mg/m^3; PAC-3: 750 mg/m^3	PAC-1 and PAC-2 based on adjustments to 1-hr TEELs; PAC-3 based on rat oral LD_{50}.	
USAPHC (air-MEG)	Gadolinium	1-hr critical: 500 mg/m^3; 1-hr marginal: 500 mg/m^3; 1-hr negligible: 500 mg/m^3	Based on TEELs; documentation of the basis for TEEL values was not located.	U.S. APHC (2013)
	$GdCl_3$ $6H_2O$	1-hr critical: 75 mg/m^3; 1-hr marginal: 75 mg/m^3; 1-hr negligible: 75 mg/m^3		
Cancer				
IRIS		NV	NA	U.S. EPA (2017)
HEAST		NV	NA	U.S. EPA (2011a)
DWSHA		NV	NA	U.S. EPA (2012)
NTP		NV	NA	NTP (2014)
IARC		NV	NA	IARC (2018)

Table 2. Summary of Available Toxicity Values for Gadolinium and Soluble Salts

Source (parameter)[a, b]	Value (applicability)	Notes	Reference
CalEPA	NV	NA	CalEPA (2011); CalEPA (2017); CalEPA (2018)
ACGIH	NV	NA	ACGIH (2016)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; USAPHC = U.S. Army Public Health Command.
[b]Parameters: LD_{50} = median lethal dose; MEG = military exposure guideline; PAC = protective action criteria; TEEL = temporary emergency exposure limit; TLV = threshold limit value; TWA = time-weighted average.

$Gd(NO_3)_3$ = gadolinium nitrate; $GdCl_3$ $6H_2O$ = gadolinium chloride hexahydrate; i.p. = intraperitoneal; NA = not applicable; NV = not available.

Non-date-limited literature searches were conducted in November 2015 and updated in February 2018 for studies relevant to the derivation of provisional toxicity values for soluble gadolinium, and primarily focused on commonly occurring forms of the compound as follows: gadolinium (CASRN 7440-54-2), gadolinium chloride (CASRN 10138-52-0), gadolinium nitrate (CASRN 10168-81-7), gadolinium acetate (CASRN 16056-77-2), gadolinium sulfide (CASRN 12134-77-9), and gadolinium bromide (CASRN 13818-75-2). 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 data: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Japan Existing Chemical Data Base (JECDB), European Chemicals Agency (ECHA), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD High Production Volume (HPV), U.S. EPA HPV, U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Office of Water (OW), U.S. EPA TSCATS2/TSCATS8e, National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and Defense Technical Information Center (DTIC). No toxicological data were located on the following compounds: gadolinium acetate (CASRN 16056-77-2), gadolinium bromide (CASRN 13818-75-2), and gadolinium sulfide (CASRN 12134-77-9); 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 gadolinium and its 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 Gadolinium and Soluble Salts							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects[c]**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[d]**
Human							
			1. Oral (mg/kg-d)				
ND							
			2. Inhalation (mg/m^3)				
ND							
Animal							
			1. Oral (mg/kg-d)				
Short-term	10 M/10 F, Slc:Wistar rat, 0, 40, 200, 1,000 mg/kg-d $GdCl_3$ $6H_2O$ by daily gavage for 28 d	0, 17, 84.7, 423 (as Gd)	Hyperkeratosis in glandular stomach, and eosinocyte infiltration in stomach (M and F); basal cell hyperplasia in forestomach and decreased serum cholinesterase (F only).	84.7[e] (as Gd)	423[e] (as Gd)	Ogawa et al. (1995); Ogawa et al. (1992) (abstract) Histopathology performed on half of animals (5/sex) in each dose group.	NPR
Subchronic	**6 M/6 F, CFN rat, 0, 0.01, 0.1, 1% $GdCl_3$ in the diet, 12 wk.**	**0, 5.38, 53.8, or 538 (M) (as Gd) 0, 6.00, 60.0, or 600 (F) (as Gd)[f]**	**Perinuclear vacuolization and coarse granular cytoplasm in parenchymal cells of the liver in 6/6 high-dose males; "not regularly observed" in lower dose males.**	**NDr**	**538 (as Gd)**	Haley et al. (1961) **Lack of incidence data for lower doses precludes determination of NOAEL.**	**PR, PS**

Table 3A. Summary of Potentially Relevant Noncancer Data for Gadolinium and Soluble Salts							
Category[a]	**Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration**	**Dosimetry[b]**	**Critical Effects[c]**	**NOAEL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[d]**
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; 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 an ADD (mg/kg-day) for oral noncancer effects. Where applicable, the dose of Gd (MW = 157.3 g/mol) was calculated from the dose of $GdCl_3$ $6H_2O$ (MW = 371.6 g/mol) or $GdCl_3$ (MW = 263.6 g/mol) by multiplying the mass percent of Gd to the reported compound dose.
[c]Critical effects are defined as statistically or biologically significant exposure-related outcomes considered for the derivation of provisional reference values.
[d]Notes: NPR = not peer reviewed; PR = peer reviewed; PS = principal study.
[e]Identified based on information presented in an abstract (Ogawa et al., 1992) and results for the similar rare earth element europium in a related study (Ogawa et al., 1995).
[f]Percent diet was converted to mg/kg-day using strain-specific food intake factors and body weights and the following equation:
ADD (mg/kg-day) = ([% diet × (1,000,000 mg/kg ÷ 100%)] × food consumption rate [kg-day]) ÷ body weight (kg).

ADD = adjusted daily dose; F = female(s); Gd = gadolinium; $GdCl_3$ = gadolinium chloride; $GdCl_3$ $6H_2O$ = gadolinium chloride hexahydrate; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); MW = molecular weight; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

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

ND = no data.

HUMAN STUDIES

No studies examining possible associations between oral exposure to soluble gadolinium and health effects in humans have been identified. The pulmonary toxicity of inhaled lanthanides, in general, has been the subject of debate, especially regarding the relative contributions of radioactive contaminants vs. stable elements in the development of progressive pulmonary interstitial fibrosis (Beliles, 1994; Haley, 1991). In particular, although it is known that stable rare earth compounds can produce a static, foreign-body-type lesion consistent with benign pneumoconiosis, 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 Bühlmann, 1975). A comprehensive assessment of the human and animal data by Haley (1991) concluded that the evidence suggests that inhalation exposure to high concentrations of stable rare earths can produce lesions compatible with pneumoconiosis and progressive pulmonary fibrosis, and that the potential for inducing these lesions is related to chemical type, physicochemical form, dose, and duration of exposure.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to gadolinium were evaluated in one short-term-duration study (Ogawa et al., 1992) and one subchronic-duration study (Haley et al., 1961).

Short-Term-Duration Studies

Ogawa et al. (1992)

Ogawa et al. (1992) reported a 28-day gavage study of gadolinium and europium chlorides in rats. This study was published only as an abstract; a full report of this study could not be located. However, the companion study of europium chloride was published (Ogawa et al., 1995) and provides study design details missing from the abstract. Gadolinium chloride hexahydrate (purity not reported) was administered in 5% glucose solution by daily gavage to Slc:Wistar rats for 28 days. Groups of 10 rats/sex/dose received 0, 40, 200, or 1,000 mg/kg-day $GdCl_3 \cdot 6H_2O$ (0, 17, 84.7, or 423 mg Gd/kg-day)[2]. Additional control and high-dose groups of the same size were treated for 28 days and then observed untreated for an additional 14 days.

Observations for mortality and clinical signs were performed twice daily, and body weights and food consumption were recorded daily throughout the study (Ogawa et al., 1995; Ogawa et al., 1992). Urine was collected during the final week of treatment for analysis of pH, occult blood, ketone bodies, glucose, and protein. At termination at the end of the treatment or recovery periods, blood was collected for hematology (red blood cell [RBC], hemoglobin [Hb], packed cell volume [PCV], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count, total and differential white blood cell [WBC] counts, prothrombin time and activated thromboplastin time), and serum chemistry (total protein, albumin, blood urea nitrogen [BUN], creatinine, uric

[2]The dose of Gd (MW = 157.3 g/mol) was calculated from the dose of $GdCl_3 \cdot 6H_2O$ (MW = 371.6 g/mol) by multiplying the mass percent of Gd to the reported compound dose.

acid, glucose, nonesterified fatty acid, triglycerides, total cholesterol, iron, unsaturated iron binding capacity, total iron binding capacity, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], cholinesterase [ChE], γ-glutamyl transferase [GGT], sodium, and chloride). Gross necropsy was performed on all animals, and the brain, heart, lungs, liver, kidneys, spleen, gonads, adrenals, salivary glands, and thymus were weighed. Half of the animals in each group (five/sex/dose) were subjected to comprehensive histopathology examination; the other half were used for determining gadolinium and iron concentration in the liver, kidneys, spleen, and bone.

Results specific to gadolinium were reported qualitatively in the abstract (Ogawa et al., 1992). Gadolinium exposure at 423 mg/kg-day resulted in decreased body weight and food consumption in both males and females (magnitude of change was not reported). In addition, female rats at this dose exhibited significant decreases in serum ChE. Iron concentrations were increased in the serum and decreased in the liver, kidney, and spleen of both sexes of rat exposed to 423 mg Gd/kg-day. At the highest dose only (423 mg Gd/kg-day), microscopic lesions were observed in the forestomach and submucosa of the stomach, consisting of hyperkeratosis and eosinophil infiltration, respectively. Analysis of organs for gadolinium content showed accumulation in the liver, femur, and kidney.

The available information on gadolinium suggest a no-observed-adverse-effect level (NOAEL) of 84.7 mg Gd/kg-day and lowest-observed-adverse-effect level (LOAEL) of 423 mg Gd/kg-day based on forestomach and stomach lesions, and decreased serum ChE. Based on the information presented in the abstract (Ogawa et al., 1992), effects associated with exposure to gadolinium were very similar to those observed with europium and occurred at the same doses.

Subchronic-Duration Studies

Haley et al. (1961)

Groups of six male and six female CFN rats were fed 0, 0.01, 0.1, or 1% dietary gadolinium chloride (purity 98%) for 12 weeks (Haley et al., 1961). Food consumption was not measured, but compound intake (adjusted daily dose [ADD] expressed as mg Gd /kg-day) is estimated to be 0, 5.38, 53.8, or 538 in the males, and 6.00, 60.0, or 600 in the females.[3]

Body weight was measured biweekly throughout the study, and hematology (total erythrocytes, total leucocytes, differential cell count, Hb, and hematocrit [Hct]) and histology (heart, lung, liver, kidney, pancreas, spleen, adrenal, and small intestine) were assessed at the end of the study.

The study authors reported that treatment did not affect growth of the rats (Haley et al., 1961). Based on visual inspection of body-weight data presented graphically, it appears that male rat body weights at the two highest doses were indistinguishable from the control weights, while body weights in males exposed to the lowest dose were ~10% lower than controls at the end of exposure. Given the lack of relationship to dose and based on the study authors' conclusions, the body-weight differences are not considered to be related to gadolinium

[3]ADD = ([(% diet × 10,000) × food consumption rate] ÷ BW) × (157.3 g/mol Gd ÷ 263.6 g/mol $GdCl_3$). Dose estimates for $GdCl_3$ were calculated using the mean reference body-weight and food-consumption rate values for all rat strains in a subchronic-duration study (U.S. EPA, 1988). Mean reference body weight: 0.235 kg (male) and 0.173 kg (female). Mean reference food consumption: 0.021 kg/day (male) and 0.017 kg/day (female).

treatment. Hematology parameters did not differ between exposed and control groups. Exposure-related changes in liver histology were observed in the males at 538 mg Gd/kg-day. The liver effects consisted of perinuclear vacuolization and coarse granular cytoplasm in parenchymal cells in 6/6 of the high-dose males; these effects were "not regularly observed" in the lower-dose male groups (incidence data not reported) and were absent in females (see Table B-1). Liver pathology findings in controls were not reported but incidences are described as "not regularly observed" and are indicative of adverse effects in the high-dose males. Assessment of the liver pathology data is complicated by the small group sizes, unreported incidences in the control, low-, and mid-dose groups, and possible effects in the low- and mid-dose groups as indicated by observations of liver lesions in some of the animals. The highest dose (538 mg Gd/kg-day) is a LOAEL based on liver pathology in males. However, given the lack of detailed information on liver pathology incidences in the low- and mid-dose groups, the aforementioned LOAEL could well be lower, and identification of a NOAEL from this study was not possible.

Chronic-Duration Studies

No studies have been identified.

Reproductive/Developmental Studies

No studies have been identified.

Inhalation Exposures

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

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Table 4A provides an overview of genotoxicity studies of gadolinium. Supporting studies on gadolinium are shown in Table 4B; these include acute oral and intraperitoneal (i.p.) lethality studies; acute- and short-term-duration studies of intravenously (i.v.) or i.p. injected gadolinium; toxicokinetic data; and mechanistic studies.

Table 4A. Summary of Gadolinium and Soluble Salts Genotoxicity

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation[a]	Results with Activation[a]	Comments	Reference
DNA strand breaks	CHO-K1 cells incubated with $GdCl_3$ for 24 hr	0, 1.4, 1.5, 1.6, 1.7 mM	+	NT	Single cell gel electrophoresis (comet) assay. $GdCl_3$ induced dose-related increases in the olive tail moment at concentrations ≥1.6 mM; cytotoxicity was observed at this and higher doses.	Grillo et al. (2014)
DNA strand breaks	Human lymphocytes exposed to $GdCl_3$ for 12 hr	0, 0.2, 0.4, 0.8 mM	+	NT	Single cell gel electrophoresis (comet) assay. $GdCl_3$ induced dose-related increases in the olive tail moment at all exposure concentrations.	Cho et al. (2014a)
MN	Human lymphocytes incubated with $GdCl_3$ for 44 hr prior to cytochalasin-B treatment for 28 hr	0, 0.4, 0.8, 1.2 mM	−	NT	CBMN assay.	Cho et al. (2014a)
Unscheduled DNA synthesis	Human peripheral lymphocytes incubated with $Gd(NO_3)_3{\cdot}nH_2O$ for 4.5 hr/d	0, 0.004, 0.008, 0.016, 0.03 mM Gd	+	NT	3H-TdR incorporation assay. $Gd(NO_3)_3{\cdot}nH_2O$ induced dose-related increases in micronucleus frequency at concentrations >0.02 mM Gd. Cytotoxicity was observed, with LC_{50} of 0.063 mM Gd in this system.	Yongxing et al. (2000)
DNA strand breaks	Human peripheral lymphocytes incubated with $Gd(NO_3)_3{\cdot}nH_2O$ for 1.5 hr	0, 0.004, 0.008, 0.016, 0.03 mM Gd	+	NT	Single cell gel electrophoresis (comet) assay. $Gd(NO_3)_3{\cdot}nH_2O$ induced dose-related increases in single strand DNA breaks at concentrations >0.02 mM Gd. Cytotoxicity was observed, with LC_{50} of 0.063 mM Gd in this system.	Yongxing et al. (2000)
MN	Human peripheral lymphocytes incubated with $Gd(NO_3)_3{\cdot}nH_2O$ for 48 hr	0, 0.016, 0.04, 0.1, 0.25, 0.625 mM Gd	+	NT	$Gd(NO_3)_3{\cdot}nH_2O$ induced dose-related increases in micronucleus frequency at concentrations ≥0.25 mM Gd. Cytotoxicity was observed, with LC_{50} of 0.063 mM Gd in this system.	Yongxing et al. (2000)

[a]+ = positive; − = negative; NT = not tested.

CBMN = cytokinesis-block micronucleus; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; $GdCl_3$ = gadolinium chloride; $Gd(NO_3)_3$ = gadolinium nitrate; LC_{50} = median lethal concentration; MN = micronuclei.

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	Reference
Studies of $Gd(NO_3)_3$				
Acute oral lethality	$Gd(NO_3)_3$ was administered orally to 20 female S-D rats; the animals were observed for 30 d.	For all of the lanthanides tested, no deaths occurred more than 4 d after exposure, and symptoms included hypoactivity and depression; no gross pathological changes were observed.	Female rat oral LD_{50} > 1,743 mg Gd/kg	Bruce et al. (1963)
Acute i.p. lethality	$Gd(NO_3)_3$ was administered i.p. to 40 female CF1 mice; the animals were observed for 30 d.	For all of 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 gadolinium were not reported.	Female mouse i.p. LD_{50} = 105 mg Gd/kg	Bruce et al. (1963)
Acute i.p. lethality	$Gd(NO_3)_3$ was administered i.p. to 40 female S-D rats; the animals were observed for 30 d.	For all of the lanthanides tested, very few rat deaths occurred within the first 8 d; most deaths occurred between the 10th and 25th d of observation. Symptoms of toxicity were not reported. Gross necropsy findings in rats exposed to all of the lanthanides included grossly distended abdomens, edema of the limbs, evidence for an inflammatory condition in the peritoneal cavity with massive adhesions, and accumulation of hemorrhagic ascitic fluid. Necropsy findings specific to gadolinium were not reported.	Female rat i.p. LD_{50} = 80 mg Gd/kg	Bruce et al. (1963)
Studies of $GdCl_3$				
Acute i.p. lethality	$GdCl_3$ was administered i.p. to male CF1 mice; the mice were observed for 7 d; no other details were provided.	The peak death rate was reached between the 4th and 5th d postexposure, but some deaths occurred at 24 hr. Symptoms of acute $GdCl_3$ toxicity included decreased respiration, lethargy, abdominal cramps, and diarrhea.; the study authors did not specify the dose levels or exposure routes leading to these effects.	Male mouse i.p. LD_{50} = 328 mg Gd/kg	Haley et al. (1961)
Acute i.p. lethality	$GdCl_3$ was administered i.p. to CFW albino mice, 6 mice per dose (sex not specified), at doses equivalent to 179 or 298 mg Gd/kg; the animals were observed for 7 d.	At 179 and 298 mg Gd/kg, 60 and 83% of the mice died respectively. Mean times to death were 75 and 41 hr, respectively.	Mouse i.p. LD_{50} = 226 mg Gd/kg	Graca et al. (1962)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	Reference
Acute i.p. toxicity	$GdCl_3$ was administered i.p. to male Kunming mice at doses of 10, 20, or 40 mg $GdCl_3$/kg (6, 12, or 24 mg Gd/kg). The animals were sacrificed 24 hr after dosing; a separate group exposed to 20 mg $GdCl_3$/kg was sacrificed at 72 and 144 hr after dosing. The number, function, and phagocytic activity of Kupffer cells were evaluated. Livers were excised for histopathology, and an analysis for ATPase activity, glycogen, NO, PGE2, cAMP, and expression of cNOS, iNOS, PKC, and nuclear transcription factors NF-κB, STAT-1, and Erk-1 was performed.	Increased serum ALT and AST, and hepatocellular swelling were noted at 24 mg Gd/kg. Kupffer cell function was decreased in a dose-dependent manner. Doses of 6 and 12 kg Gd resulted in apoptosis of Kupffer cells; at 24 mg Gd/kg, disruption of Kupffer cell membranes was seen. $GdCl_3$ exposure resulted in decreases in NO, PGE, and cAMP at ≤12 mg Gd/kg, and a significant increase at 24 mg Gd/kg. $GdCl_3$ exposure inhibited expression of cNOS, PKC, and NF-κB.	Exposure to $GdCl_3$ selectively blocked Kupffer cell activity at doses ≤12 mg Gd/kg and caused toxicity at 24 mg Gd/kg.	Ding et al. (2003)
Acute i.v. toxicity	$GdCl_3$ was administered i.v. to 10 cats/sex/dose (strain not reported) at doses equivalent to 3, 6, 18, or 30 mg Gd/kg. Cardiovascular responses were examined 2 hr later.	No effects occurred at doses up to 6 mg Gd/kg. At 18 mg Gd/kg, transient hypotension and a decrease in femoral blood flow were seen; in addition, complete cardiovascular collapse occurred at this and higher doses (mortality, if observed, was not reported).	At i.v. doses ≥18 mg Gd/kg, cardiovascular effects were seen in cats.	Haley et al. (1961)
Acute i.v. toxicity	$GdCl_3$ hexahydrate was administered i.v. to 10 S-D rats/sex/dose at doses equivalent to 0 or 11 mg Gd/kg. Plasma calcium and phosphate concentrations, as well as stomach histopathology, were evaluated at regular intervals up to 24 hr (plasma) and 56 d (histopathology) after dosing.	Plasma calcium and phosphate concentrations doubled in the 12 hr after dosing. Histopathology findings in the stomach consisted of progressive mineralization of the lamina propria, accompanied by mucous cell hyperplasia, interstitial fibrosis, and sparse infiltration of inflammatory cells. X-ray microanalysis of the mineral deposits revealed calcium and phosphate (as hydroxyapatite), with little to no gadolinium. The study authors suggested that these findings were indicative of metastatic mineralization, in which calcium salts are deposited in tissues due to increased serum levels of calcium.	$GdCl_3$ increased serum calcium and phosphate concentrations in rats, leading to metastatic mineralization.	Rees et al. (1997)
Acute i.v. toxicity	$GdCl_3$ was administered i.v. to male C57BL/6J mice at doses equivalent to 0 or 30 mg Gd/kg. 24 hr later, the mice received MRI examinations before and after administration of ferumoxide to measure Kupffer cell activity.	Exposure to $GdCl_3$ modestly inhibited Kupffer cell activity without causing hepatocellular damage.	Exposure $GdCl_3$ inhibited Kupffer cell activity in mice.	Fabre et al. (2010)

Table 4B. Supporting Toxicity Studies

Test	Materials and Methods	Results	Conclusions	Reference
Acute i.v. toxicity	$GdCl_3$ was administered i.v. to male CD-1 Out-bred Albino mice at doses equivalent to 0, 1.5, or 5.0 mg Gd/kg daily for 14 d. At sacrifice at the end of exposure, hematology and clinical chemistry (BUN, creatinine, AST, ALT, ALP, bilirubin) were evaluated. The kidney, spleen, and liver were examined microscopically. Electron probe microanalysis was used to assess subcellular localization of gadolinium in high-dose mice.	Increased ALT, AST, and ALP were observed at the highest dose. Hematology was not affected. Histopathology in the liver consisted of mild, multifocal hepatocellular degeneration and necrosis with scant neutrophil and mononuclear cell infiltration; the affected dose group(s) were not reported. Granules containing gadolinium occurred often in the Kupffer cells and in the bile canaliculi. In the kidney, granules containing gadolinium were observed in phagolysosomes within glomerular mesangial cells. In the spleen, gadolinium granules were located in macrophages and neutrophils.	Exposure to $GdCl_3$ led to evidence of liver toxicity in mice.	Wasserman et al. (1996)
Acute i.v. toxicity	$GdCl_3$ was administered i.v. to male S-D rats at doses equivalent to 0 or 6 mg Gd/kg. 24 hr later, hepatic microcirculation was evaluated and serum TNFα, IL-6, and AST activities were assessed.	Exposure to $GdCl_3$ resulted in a significant decrease in Kupffer cell phagocytic activity, increased serum cytokine (TNFα and IL-6), ALT and AST activities, and reduced bile flow and microvascular perfusion, without histopathology changes in the liver.	$GdCl_3$ exposure inhibited Kupffer cell activity at exposures that do not result in histopathology changes.	Rüttinger et al. (1996)
Acute toxicity after intratracheal instillation	$GdCl_3$ was administered by intratracheal instillation to male Wistar rats at doses of 0, 10, 20, 50, or 100 µg/rat Gd. The animals were sacrificed 2 d after dosing for evaluation of BALF for calcium and potassium concentration, ELF volume, protein concentration, LDH activity, total nucleated cell count, and differential cell count.	Exposure to $GdCl_3$ resulted in dose-related increases in LDH activity, protein concentration, ELF volume, and calcium content in BALF. Numbers of neutrophils and eosinophils were increased by exposure to $GdCl_3$, while numbers of alveolar macrophages were decreased.	Exposure to $GdCl_3$ altered BALF.	Yoneda et al. (1995)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATP = adenosine triphosphate; BALF = bronchoalveolar lavage fluid; BUN = blood urea nitrogen; cAMP = cyclic adenosine monophosphate; cNOS = constitutive nitic oxide synthase; ELF = epithelial lining fluid; $GdCl_3$ = gadolinium chloride; $Gd(NO_3)_3$ = gadolinium nitrate; i.p. = intraperitoneal; iNOS = inducible nitric oxide synthase; i.v. = intravenous; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NF-κB = nuclear factor kappa-light-chain enhancer of activated B cells; NO = nitric oxide; PGE = prostaglandin E; PKC = protein kinase C; S-D = Sprague-Dawley.

These studies indicated the following:

- Genotoxicity data are limited, but suggest that gadolinium chloride and gadolinium nitrate may induce deoxyribonucleic acid (DNA) strand breaks and/or unscheduled DNA synthesis (Cho et al., 2014a; Grillo et al., 2014; Yongxing et al., 2000).

- An acute-duration toxicity study demonstrated limited oral absorption of gadolinium chloride and gadolinium nitrate in mice (Bruce et al., 1963) and suggested slightly greater sensitivity of guinea pigs, compared with mice, to gadolinium chloride lethality (Graca et al., 1962). Acute toxicity studies demonstrated that gadolinium chloride administered intravenously can impair blood clotting (Spencer et al., 1998; Graca et al., 1964); increase ALT and AST (Ding et al., 2003; Wasserman et al., 1996); lead to a number of lesions in both rats and mice including mineral emboli in capillaries, hepatocellular necrosis, mineral deposits in the mononuclear phagocytic system and spleen, and lymphoid depletion and necrosis in the spleen (Spencer et al., 1998; Spencer et al., 1997); and also induce mineralization of the glandular mucosa in the stomach, in rats (Spencer et al., 1998).

- Gadolinium is expected to be poorly absorbed through the gastrointestinal (GI) tract [as reviewed by Leggett et al. (2014)]. Once absorbed, gadolinium is deposited in bone, liver, kidney, and lung [as reviewed by Leggett et al. (2014)]. Data on excretion of gadolinium are not available, but other lanthanides are excreted primarily via feces (Nakamura et al., 1991).

- Mechanistic data on gadolinium are limited, but show that gadolinium may affect the liver via inhibition of Kupffer cell activity (Korolenko et al., 2008) and/or induction of reactive oxygen species (ROS) (Ye et al., 2013; Ye et al., 2011). Gadolinium is also known to disrupt calcium homeostasis (Palasz and Czekaj, 2000; Rees et al., 1997; Yoneda et al., 1995), potentially affecting a wide variety of calcium-mediated signaling pathways.

More detailed descriptions of these data are presented below.

Genotoxicity

Gadolinium chloride has been tested in vitro for induction of micronuclei (MN) in human lymphocytes and for DNA strand breaks in human lymphocytes and Chinese hamster ovary (CHO)-K1 cells. This compound did not induce an increased frequency of MN (Cho et al., 2014a), but did yield positive results when tested for DNA strand breaks (Cho et al., 2014a; Grillo et al., 2014). Gadolinium nitrate hydrate tested positive for MN, DNA strand breaks, and unscheduled DNA synthesis in human lymphocytes; however, an increased frequency of MN was only observed at concentrations that were cytotoxic (Yongxing et al., 2000).

Acute Toxicity Studies

In the only acute oral exposure study identified, the oral median lethal dose (LD_{50}) for gadolinium nitrate was >1,743 mg Gd/kg in female rats observed for 30 days postdosing (Bruce et al., 1963).

Supporting Toxicity Studies

Acute lethality studies of gadolinium are shown in Table 4B. Acute i.p. LD_{50} values of 80 and 105 mg Gd/kg were reported for female rats and mice, respectively, exposed to gadolinium nitrate and observed for 30 days (Bruce et al., 1963). Unlike the mice, the rats succumbed to gadolinium nitrate exposure much later, with most rat deaths occurring between 10–25 days postdosing (Bruce et al., 1963). Acute i.p. LD_{50} values of 226 and 328 mg Gd/kg were reported for gadolinium chloride in male mice observed for 7 days (Graca et al., 1962; Haley et al., 1961). Symptoms of acute gadolinium chloride toxicity in mice included decreased respiration, lethargy, abdominal cramps, and diarrhea (Haley et al., 1961).

As shown in Table 4B, studies of $GdCl_3$ administered as single i.v. doses have demonstrated effects of gadolinium on blood pressure of cats (Haley et al., 1961), plasma calcium and phosphate concentrations and histopathology in rats (Rees et al., 1997), and liver function and pathology in rats and mice (Fabre et al., 2010; Ding et al., 2003; Rüttinger et al., 1996; Wasserman et al., 1996). After intratracheal instillation of gadolinium chloride in rats, an increase in the calcium content of bronchoalveolar lavage fluid (BALF) was observed (Yoneda et al., 1995). Acute toxicity studies evaluating multiple outcomes (Spencer et al., 1998; Spencer et al., 1997; Graca et al., 1964) are not presented in the table, but are instead discussed below.

Graca et al. (1964) investigated the effects of intravenously administered chloride salts of lanthanide elements on heart rate, blood pressure, respiration, and clinical hematology in male and female dogs (breed/number/sex not specified). Aqueous solutions of the chlorides (equivalent to 5% of the chloride) of 15 lanthanide elements were injected into a cannula inserted into the left femoral vein. Ten doses of 10 mg $GdCl_3$/kg (6 mg Gd/kg) each were injected under anesthesia at 10-minute intervals. For each lanthanide element, groups of three dogs were treated with the chloride. Three groups of control dogs were injected with sodium citrate (n = 6), ammonium versenate (n = 6), or Ringer's solution (n = 12) in the same manner as the treated animals. Blood samples were collected from the right femoral vein before treatment and 0, 10, 30, 60, 100, and 160 minutes after treatment for analysis of erythrocyte, leukocyte and differential cell counts, prothrombin and coagulation time, Hb, sedimentation, and Hct. After 160 minutes, the animals were necropsied and tissues were collected for histopathology (liver, spleen, kidney, lung, sternum, mesentery lymph nodes, heart, adrenal, and ovaries or testes). Heart rate, respiration, and blood pressure readings were made at the same intervals as blood samples.

Results for the 15 elements were discussed generally and presented graphically as change over time after treatment (Graca et al., 1964). Some animals died from treatment (14/45 treated with chlorides), but the mortality was not reported by element. Gadolinium chloride had minimal to no apparent effect on blood pressure or heart and respiratory rates, but it increased prothrombin time (to >100 seconds by 60 minutes after treatment, compared to a maximum of 10 seconds for control animals) and coagulation time (to >55 minutes by 30 minutes after treatment, compared with a maximum of about 10 minutes for control animals). The effect on clotting parameters was generally consistent among almost all of the lanthanide elements. Visual observation of pooled blood at incision sites provided additional evidence of the effect of lanthanide elements on clotting parameters, but the study authors did not report the incidence or the specific treatment group(s) in which this was observed. Gross and histopathological examinations revealed slight to moderate hyperemia of the lungs, only in animals treated with chlorides of the lanthanide elements.

Spencer et al. (1998) and Spencer et al. (1997) evaluated the effects of single i.v. doses of gadolinium chloride hexahydrate (purity 99.9%) on Sprague-Dawley rats and CD-1 mice. In the rat study (Spencer et al., 1997), the test material was administered to groups of 10 animals/sex/dose at doses of 0, 0.07, 0.14, or 0.35 mmol $GdCl_3 \cdot 6H_2O$/kg (equivalent to doses of 0, 11, 22, and 55 mg Gd/kg). Half of the animals in each group were sacrificed 48 hours after dosing and the other half were sacrificed 14 days after dosing. Body weights were measured at regular intervals and just prior to sacrifice. Blood was collected at autopsy for evaluation of hematology (including clotting parameters) and serum chemistry. At sacrifice, all animals were necropsied and the kidneys, liver, lung, ovaries, spleen, testes, and thymus were weighed. Histopathology examinations of the adrenal glands, bone marrow, heart, kidneys, liver, lung, spleen, stomach, and thymus were performed; alizarin red staining was used to evaluate tissue mineralization.

One female rat died immediately after receiving a dose of 55 mg Gd/kg; another female and one male exposed to this dose were prostrate for 2 minutes after dosing (Spencer et al., 1997). Body-weight gain was significantly lower (≥20%) in male rats exposed to 22 and 55 mg/kg. Exposure to gadolinium resulted in significant hematology changes (increases in WBC, polymorphonuclear leukocyte and lymphocyte counts, and significantly decreased platelet count, and increased activated partial thromboplastin time [APTT]) and serum chemistry alterations (increased cholesterol, ALP, triglycerides, and potassium; decreased glucose; and increased BUN and bilirubin [in males only]). While not statistically significant, ALT and AST were more than twice the control values at the mid and high doses in both males and females. Significant increases in liver, kidney, and spleen weights were seen in both sexes at all doses; lung weight was also increased, but the report did not state the dose at which this effect was seen. Treatment-related histopathology changes were observed in the liver, spleen, bone marrow, thymus, lung, stomach, kidney, and adrenal glands when assessed 2 days after dosing. In the kidneys, mineral deposits in the capillaries were seen in rats exposed to 22 and 55 mg Gd/kg, and at the highest dose, multifocal necrosis of the proximal convoluted tubules was noted in 3/5 females. In the liver, necrosis, sometimes accompanied by hemorrhage and/or dystrophic calcification, was observed in male rats exposed to ≥22 mg Gd/kg. Kupffer cells, and some hepatocytes, contained basophilic mineral deposits. In addition, mitotic activity was increased in hepatocytes and Kupffer cells. It was not clear from the report whether female rats also exhibited hepatic lesions. In the group examined 14 days after dosing, there was no necrosis, but multifocal chronic inflammation, occasionally accompanied by giant cells and fibrosis, was observed in the liver at all doses.

Interstitial mineralization in a band around the neck of the gastric gland was the predominant lesion in the stomach. At the lowest dose, mineralization was seen as a continuous band, while at higher doses, discrete foci were seen (Spencer et al., 1997). Inflammatory cells and/or fibroblasts were occasionally seen with the mineral deposits. Epithelial cells displayed increased mitosis, and petechial hemorrhages were occasionally observed beneath mucous cells. Fourteen days postdosing, many of the changes remained and were accompanied by thickening of the neck of the gastric gland with hyperplasia of mucous cells.

In the mouse study (Spencer et al., 1998), groups of five male and five female mice received single i.v. doses of 0, 0.05, 0.1, and 0.2 mmol $GdCl_3 \cdot 6H_2O$/kg (equivalent to doses of 0, 8, 16, and 31 mg Gd/kg). The mice were sacrificed 24 hours after dosing, whereupon blood samples were obtained for serum chemistry, and organ weights (liver, kidneys, lung, spleen,

gonads, and thymus) were measured. All animals were necropsied, and microscopic examinations of the heart, kidneys, liver, lung, spleen, stomach, and thymus were performed. Serum chemistry changes related to treatment included increased cholesterol, globulin, and lactate dehydrogenase (LDH); serum calcium was also increased at the highest dose in males only. Organ-weight changes included increased liver (males, 8−12% higher than controls) and spleen weights (males and females, up to 65 and 35% higher than controls, respectively) at the mid and high doses, and increased lung weight in males and females (68 and 28% higher than controls, respectively) at the highest dose. Histopathology findings were noted in the spleen, liver, lung, kidney, stomach, heart, and thymus. At the lowest dose, there were scattered foci of necrosis in the spleen, as well as mineralization in the marginal zone of the white pulp and loss of lymphocytes in this area of the spleen; in addition, two males exhibited mineral deposits in the Kupffer cells at this dose. At higher doses, all animals exhibited these splenic and liver lesions, with more extensive lymphocyte depletion in the spleen. Multifocal coagulative necrosis was observed in the liver of one high-dose female. Mineral deposits in the alveolar capillaries of the lung were observed in males at all doses and in mid- and high-dose females; there was, however, no evidence of degenerative or inflammatory conditions associated with these deposits. Mineral deposits were also noted in the capillaries of the kidneys of all high-dose mice and in the stomach of 4/5 high-dose females. The highest dose of gadolinium chloride also induced changes in the heart (foci of inflammation and faint basophilic granular material in the intraventricular septum) and thymus (lymphocytolysis and mild cortical atrophy).

An implantation study was performed in which groups of 30 male and 30 female weanling CFW mice received subcutaneous (s.c.) implantations of 200 mg pellets of gadolinium (1.5−2.0 mm diameter) and observed for life (an average of 9.7−16.1 months for the various cohorts) (Ball et al., 1970). Comparison with 16 male and 16 female sham-implanted controls showed no clear treatment-related induction of local sarcomas. Incidences of implantation-sited sarcomas were 1/30 and 0/16 in treated and control males, respectively, and 2/30 and 0/16 in treated and control females, respectively. No tumor metastases were observed. Implantation-site granulomas that were indicative of a foreign-body reaction developed in treated mice (15/30 males, 18/30 females) but not in controls.

Metabolism/Toxicokinetic Studies

The oral absorption of gadolinium and other lanthanide elements is very low, probably because these elements form insoluble hydroxides at neutral pH. While an estimate of the GI absorption of gadolinium 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 [as 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 gadolinium 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 gadolinium concentrations were in the rib and lung (14 nmol/kg fresh weight each), followed by thyroid and thymus (4.1 nmol/kg), stomach (3.6 nmol/kg), liver

(2.9 nmol/kg) and muscle, skin, and adrenal gland (each at 2.1 nmol/kg); other tissues and blood had lower concentrations. Leggett et al. (2014) indicated that the data were very uncertain due to potential errors in measuring low concentrations and the high variability in the measured concentrations.

Distribution and retention of gadolinium after oral exposure have not been studied. After intratracheal instillation of gadolinium chloride in male Wistar rats, gadolinium was deposited in lung tissue at levels that declined very slowly, with a half-life of about 136 days (Yoneda et al., 1995). One day after intramuscular injection of radioactive gadolinium oxides (chelated in citrate solution to increase the speed of absorption) to rats, approximately 15% of the absorbed dose of ^{159}Gd was excreted, ~45% was deposited in bone, and ~25% was deposited in liver (remaining 15% was not quantified by tissue) (Durbin et al., 1956). Long-term retention of gadolinium has not been studied; however, Durbin et al. (1956) estimated that the half-life for elimination of europium (a lanthanide close to gadolinium in the series) from the skeleton was about 2.5 years, based on data collected over 256 days.

Dean et al. (1988) evaluated the pharmacokinetics of intravenously injected gadolinium chloride in the rat. Animals were sacrificed at intervals up to 1 hour after injection for measurement of soft tissue gadolinium content. After exposure, the initial gadolinium concentration in blood was ~1.5 µmol/g, and declined slowly over the course of the hour, ending at about 0.5 µmol/g. The highest tissue concentration occurred in the lungs, where a concentration approaching 2.0 µmol/g was seen immediately after exposure; the concentration declined to about half that over the course of the hour postexposure. In the liver, spleen, and adrenal glands of rats exposed to gadolinium chloride, gadolinium concentrations increased steadily over the observation period, with spleen concentration increasing at a faster pace than liver or adrenal glands; measurements at 1 hour postdosing were ~1.7, ~1.4, and ~0.75 µmol/g in the spleen, liver, and adrenal glands. In the renal cortex, the peak concentration of ~0.25 µmol/g occurred immediately after exposure, with a very slow decline over the remaining hour of observation. According to the study authors, the preferential distribution of gadolinium chloride to the lung, spleen, liver, and adrenals suggested that this compound formed insoluble compounds with carbonates and phosphates in the blood, and was distributed via the reticuloendothelial system.

Data on the excretion of gadolinium after exposure of humans or animals were not located. 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/kg lanthanide) was excreted in the feces within 7 days [Nakamura et al. (1991), published in Japanese with English abstract and tables]. Elimination of gadolinium is likely to follow a similar pattern.

Mechanistic Studies

Available data do not provide a clear picture of the mechanisms involved in gadolinium-induced liver toxicity. Gadolinium is well known to inhibit Kupffer cell activity, an effect that may protect against hepatotoxicity induced by other xenobiotics (e.g., cadmium and radiation) (Kyriakou et al., 2013; Du et al., 2010). However, inhibition of Kupffer cells by gadolinium pretreatment has been shown to increase the severity of cholestasis in mice exposed to α-naphthylisothiocyanate (Korolenko et al., 2008), demonstrating that this inhibition is not always beneficial. Information on the potential role of ROS in gadolinium-induced

hepatotoxicity is also somewhat conflicting. Ye et al. (2011) reported that gadolinium chloride increased intracellular ROS and induced apoptosis in normal human liver embryo cells in vitro, while the same study authors (Ye et al., 2013) observed apoptosis without increased ROS in immortalized HepG2 cells. However, it is possible that the high level of basal ROS in HepG2 cells may have masked an increase (Ye et al., 2013).

Gadolinium exposure has been shown to disrupt calcium homeostasis, a perturbation that could lead to a variety of downstream effects. In vitro studies demonstrate that gadolinium inhibits calcium channels, blocks calcium-dependent enzymes, and alters the balance of intra- and extracellular calcium concentrations [reviewed by Palasz and Czekaj (2000)]. Studies in rats and mice exposed intravenously or by intratracheal instillation provide evidence that gadolinium can perturb calcium homeostasis in vivo as well. Spencer et al. (1998) observed significantly increased serum calcium in male mice given a single i.v. dose of gadolinium chloride. Similarly, Rees et al. (1997) reported that plasma calcium concentrations in rats doubled in the 12 hours after a single i.v. dose of gadolinium chloride. In rats treated by intratracheal instillation of $GdCl_3$, a dose-related increase in calcium content was observed in BALF (Yoneda et al., 1995).

Gadolinium-Based MRI Contrast Agents

Due to its paramagnetic properties, gadolinium is used in a variety of MRI contrast agents to enhance signal intensity. In order for gadolinium to be used as an MRI contrast agent, it is first bound within a chelating agent to inhibit direct toxicity from the free gadolinium ion. Gadolinium-based contrast agents (GBCAs) are administered intravenously. However, the distribution and tissue availability of gadolinium from GBCAs administered intravenously differs markedly from those of gadolinium taken up after oral or inhalation exposure. To this point, the kidney appears to be the target organ of i.v. GBCA administration, while the liver and lungs appear to be affected by dietary and inhalation exposures to gadolinium salts. This is mainly because gadolinium compounds are poorly absorbed by the respiratory and GI tracts. Further, i.p. and i.v. exposure to gadolinium salts appears to affect the liver, while similar administration of the chelated GBCA does not. Nevertheless, information on the adverse effects of these agents is included both for completeness and to demonstrate the differing toxicological properties of the two forms of gadolinium.

There are a number of commercially available GBCAs, including gadodiamide, gadoversetamide, gadobenate deglumine, gadoteridol, gadopentetate deglumine, gadoterate meglumine, gadobutrol, gadoxetic acid disodium salt, and gadofosveset. The chelate moiety is intended to inhibit release of the gadolinium ion to the biological system and facilitate clearance of the compound from the body. While the chelates are generally stable in physiological systems, dissociation and release of Gd^{3+} ions is possible with any of the available compounds (Todd and Kay, 2008). Endogenous cations (including calcium, copper, iron, and zinc) may compete with gadolinium for chelation binding sites through a process called transmetallation, leading to the release of gadolinium ions (Brambilla et al., 2008; Todd and Kay, 2008). By the same process, physiological anions, such as phosphate, carbonate, hydroxyl, and citrate, can compete with the chelating agent for binding to gadolinium (Abraham et al., 2008).

Human exposure to gadolinium by i.v. injection occurs when GBCAs are used to enhance the clarity of MRIs or magnetic resonance angiography (Rogosnitzky and Branch, 2016). In patients with impaired renal function, exposure to GBCAs has been associated with the

development of nephrogenic systemic fibrosis (NSF) [reviewed by Rogosnitzky and Branch (2016); Bernstein et al. (2012)], a severe and disabling condition characterized by fibrosis of the skin and internal organs, and resembling scleroderma or scleromyxedema (Todd and Kay, 2008). In a few case reports, effects other than NSF (including acute renal failure, pancreatitis, and encephalopathy) have been reported in humans exposed to GBCAs [reviewed by Rogosnitzky and Branch (2016)]. Bernstein et al. (2012) summarized epidemiological and mechanistic evidence indicating that the gadolinium ion, and not the chelating agent, is the cause of NSF. Particularly compelling are the data showing detectable gadolinium in the affected tissues of NSF patients, and that GBCAs with lower stability (i.e., from which gadolinium ions more readily dissociate) were more likely to induce NSF. NSF is thought to occur in patients with severe renal dysfunction due to slower renal clearance of GBCAs, enabling dissociated gadolinium to accumulate in tissues. However, more recently, it has been shown that gadolinium from GBCAs is also retained in tissues of patients with normal renal function (Rogosnitzky and Branch, 2016). Recent evidence describes bone, skin, and s.c. tissue pain with progressive thickening and discoloration of the skin in patients exposed to GBCAs with normal renal function (Semelka et al., 2016). This constellation of symptoms has recently been termed "gadolinium deposition disease" and is hypothesized to be the result of an immunologic response to GBCA exposure.

A number of recent studies in both humans and rodents have demonstrated that i.v. exposure to GBCAs results in deposition of gadolinium in the brain and bone [reviewed by Rogosnitzky and Branch (2016)]. For example, in autopsies of patients with normal renal function who were exposed to GBCAs, there was preferential accumulation of gadolinium in the dentate nucleus and globus pallidus of the brain [Kanda et al. (2015a) and Stojanov et al. (2016) as cited in Rogosnitzky and Branch (2016)]. Gadolinium deposited in bone may persist for years [reviewed by Rogosnitzky and Branch (2016)]; samples of femoral head bone from patients undergoing hip replacement showed elevated gadolinium concentrations as long as 8 years after exposure to GBCAs. Both brain and bone tissue accumulation of gadolinium was higher in patients exposed to GBCAs with higher dissociation constants (greater propensity to release free gadolinium), suggesting that the deposited material could be free (or transmetallated), rather than chelated, gadolinium [reviewed by Rogosnitzky and Branch (2016)].

Comparative pharmacokinetic data show stark differences in the uptake and distribution of GBCAs compared with gadolinium chloride. In rats intravenously exposed to ^{143}Gd as gadopentetate deglumine, gadolinium concentrations in blood, liver, lungs, adrenal glands, and spleen dropped rapidly in the first 5 minutes and declined to almost nondetectable levels within 1 hour (Dean et al., 1988). In contrast, when administered intravenously as the chloride, the initial gadolinium concentration in blood was almost three times higher than after gadopentetate deglumine administration, and declined slowly over the course of the hour. In the liver, spleen, and adrenal glands of rats exposed to i.v. gadolinium chloride, gadolinium concentrations increased steadily over the 1-hour observation period, with spleen concentration increasing at a faster pace than liver or adrenal glands. Renal levels of gadolinium differed between the two exposures; initial renal levels were much lower with exposure to $GdCl_3$ (~0.25 µmol/g) than gadopentetate deglumine, and declined slowly, while renal levels spiked to ~1.25 µmol/g shortly after exposure to gadopentetate deglumine, declining rapidly thereafter. The study authors suggested that the lower blood concentration and higher initial renal levels after exposure to the gadopentetate deglumine likely reflect rapid diffusion through the capillaries into extravascular spaces and excretion by the kidneys (Dean et al., 1988). In contrast, the distribution of $GdCl_3$ to

lung, spleen, liver, and adrenals suggested precipitation in the blood and uptake by the reticuloendothelial system (Dean et al., 1988).

Mechanisms underlying NSF in patients with renal impairment treated with GBCAs have been proposed. In a review, Todd and Kay (2008) suggested that renal dysfunction leads to dissociation of gadolinium from the chelate and deposition in tissues, localized cytotoxicity, and recruitment of profibrotic and proinflammatory cells, induction of cytokines or chemokines, and increased collagen production. Support for many of these events comes from in vitro studies [reviewed by Rogosnitzky and Branch (2016); Bernstein et al. (2012)]. An alternative mechanism may involve free gadolinium ions forming insoluble salts with phosphates and carbonates that are taken up by the phagocytic system, also triggering a fibrotic response [reviewed by Brambilla et al. (2008)]. Finally, iron mobilization may also play a role in the development of NSF; in nephrectomized mice, coexposure to an iron chelator with gadopentetate deglumine significantly mitigated the development of dermal fibrosis compared with gadopentetate deglumine alone (Bose et al., 2015). The degree to which iron mobilization is attributable to the gadolinium ion vs. the chelate complex is unknown; however, it is noteworthy that iron concentrations were increased in the serum and decreased in the liver, kidney, and spleen of rats exposed to gadolinium chloride hexahydrate by gavage for 28 days (Ogawa et al., 1992).

In summary, the most well-studied adverse effect of GBCAs in humans exposed intravenously is NSF, and available information provides evidence that the gadolinium ion plays a role in the mechanism of action leading to this endpoint. However, the uptake and distribution of intravenously administered GBCAs differs substantially from those observed after oral exposure to gadolinium salts.

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer references values, respectively, for soluble gadolinium. As a result of the uncertainties in the available data for soluble gadolinium, subchronic and chronic provisional reference doses (p-RfDs) are not derived. The available data may be used, however, in the derivation of a screening subchronic p-RfD (see Appendix A). In light of the lack of information on relative oral toxicity of soluble gadolinium compounds, available data support derivation of only a screening subchronic p-RfD for soluble gadolinium.

Table 5. Summary of Noncancer Reference Values for Gadolinium and Soluble Salts

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HED)	UF_C	Principal Study
Screening Subchronic p-RfD for soluble gadolinium (mg Gd/kg-d)	Rat/M	Perinuclear vacuolization and cytoplasmic granularity in the liver	4×10^{-2} (derived in Appendix A)	LOAEL	129	3,000	Haley et al. (1961)
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

Gd = gadolinium; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; 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 6. Summary of Cancer Reference Values for Gadolinium and Soluble Salts

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

The available human and animal data are not considered sufficiently reliable to use in deriving subchronic or chronic p-RfDs for soluble gadolinium. Information on the toxicity of repeated oral exposure to soluble gadolinium is limited to one short term gavage study [results reported in Ogawa et al. (1995) and methodology details reported in Ogawa et al. (1992)] and a single subchronic-duration dietary study of gadolinium chloride in rats (Haley et al., 1964). The short term study (Ogawa et al., 1995; Ogawa et al., 1992) was published only as an abstract, and a full report of the study could not be located. In contrast, the Haley et al. (1961) study is a peer-reviewed report using three dose groups plus a control group, but group sizes were relatively small (6/sex/group), and there was a lack of comprehensive endpoint evaluation, with clinical chemistry, organ weights, urinalysis, and histopathology of potentially sensitive organs

(i.e., stomach, forestomach) not performed. Additionally, Haley et al. (1961) did not report control incidences, which further lessened the confidence in this study. Consequently, a NOAEL was not identified. Additional studies investigating the genotoxicity of gadolinium chloride and gadolinium nitrate suggest that these compounds may be capable of inducing DNA strand breaks and/or unscheduled DNA synthesis (Cho et al., 2014a; Grillo et al., 2014; Yongxing et al., 2000; Bruce et al., 1963) in vitro. Acute studies of i.v. or i.p. exposure to gadolinium chloride in mice, rats, and cats were identified, but are limited in scope (Fabre et al., 2010; Ding et al., 2003; Rees et al., 1997; Rüttinger et al., 1996; Wasserman et al., 1996; Yoneda et al., 1995; Graca et al., 1962; Haley et al., 1961). As a result of the uncertainties in the available data for soluble gadolinium, subchronic and chronic p-RfDs are not derived. The available data may be used, however, in the derivation of a screening subchronic p-RfD (see Appendix A). In light of the lack of information on relative oral toxicity at the low and mid doses of soluble gadolinium compounds, available data support derivation of only a screening subchronic p-RfD for soluble gadolinium.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

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

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

No adequate studies evaluating carcinogenicity effects in humans or animals exposed to soluble gadolinium are available. Subcutaneous implantation of a gadolinium pellet caused no clear treatment-related increase in the incidence of local sarcomas or metastases in mice observed for life (Ball et al., 1970). Genotoxicity data for gadolinium are limited, but show that soluble gadolinium salts may induce unscheduled DNA synthesis, DNA strand breaks, and MN (Cho et al., 2014b; Grillo et al., 2014; Yongxing et al., 2000). The cancer weight-of-evidence (WOE) descriptor for gadolinium is presented in Table 7.

Table 7. Cancer Weight-of-Evidence Descriptor for Gadolinium and Soluble Salts

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 adequate studies evaluating carcinogenicity effects in humans or animals exposed to gadolinium are available.**
"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 gadolinium is precluded by the lack of data demonstrating carcinogenicity associated with gadolinium exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

For the reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, toxicity data for gadolinium and salts are inadequate to derive noncancer provisional toxicity values or assess the carcinogenicity of these substances. However, information is available for this chemical, which although insufficient to support deriving a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with deriving an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

DERIVATION OF A SCREENING SUBCHRONIC PROVISIONAL REFERENCE DOSE

Information on the toxicity of repeated oral exposure to soluble gadolinium is limited to a single subchronic-duration dietary study of gadolinium chloride in rats (Haley et al., 1961) and a 28-day gavage study of gadolinium chloride available only as an abstract (Ogawa et al., 1992). The subchronic-duration dietary study by Haley et al. (1961) is selected as the principal study, and liver lesions, specifically hepatic perinuclear vacuolization and cytoplasmic granularity, are identified as the critical effect.

The 12-week rat dietary study by Haley et al. (1961) is a peer-reviewed study that evaluated more than one dose. However, uncertainty remains due to the lack of quantitative data reporting and the lack of comprehensive endpoint evaluation; clinical chemistry, organ weights, urinalysis, and histopathology of potentially sensitive organs (i.e., stomach, forestomach) were not performed. A lowest-observed-adverse-effect level (LOAEL) of 538 mg Gd/kg-day was identified based on liver lesions; at this dose, all (6/6) male rats exhibited hepatic perinuclear vacuolization and cytoplasmic granularity. Liver lesions at the low and mid doses were "not regularly observed," but incidences were not reported. The ambiguity of the reported result precludes identification of a no-observed-adverse-effect level (NOAEL). Additionally, due to incomplete reporting of the study results, relevant statistically significant histopathological changes at the low and mid doses cannot be determined, which precludes identification of a potential LOAEL in the low- and mid-dose groups and increases the uncertainty of the point of departure (POD). The 28-day study of gadolinium chloride by Ogawa et al. (1992) was available only as an abstract, and is therefore not selected as the principal study, although information from a published companion study of europium chloride (Ogawa et al., 1995) was available to clarify methodology and study design. Although inadequately characterized, these studies describe increased serum cholinesterase levels (in the absence of histopathological liver changes) after oral gavage administration of gadolinium. To further support identification of the liver as a primary target of toxicity, effects were also observed following exposure to gadolinium via other exposure routes (i.e., intravenously [i.v.] and intraperitoneal [i.p.]). In this context, functional and histopathological changes were observed in the livers of gadolinium-treated mice and rats (via i.v. or i.p. exposure), including increased alanine transferase (ALT) and aspartate

aminotransferase (AST), increased liver weight, and increased incidence of necrosis (Ding et al., 2003; Spencer et al., 1998; Spencer et al., 1997; Wasserman et al., 1996).

The LOAEL of 538 mg Gd/kg-day in male rats from the subchronic-duration dietary study by Haley et al. (1961) is selected as the POD for derivation of a screening subchronic provisional reference dose (p-RfD). The LOAEL is converted to a human equivalent dose (HED) according to current U.S. EPA (2011b) guidance. In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an oral reference dose (RfD) from effects that are not portal-of-entry effects. As the critical effect for gadolinium (liver lesions) is not a portal-of-entry effect, body-weight scaling is appropriate.

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

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

where

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

Using a reference BW_a of 0.235 kg for rats and a reference BW_h of 70 kg for humans, the resulting DAF is 0.24 (U.S. EPA, 2011b). Applying this DAF to the LOAEL of 538 mg Gd/kg-day yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{LOAEL (mg Gd/kg-day)} \times \text{DAF} \\ &= 538 \text{ mg Gd/kg-day} \times 0.24 \\ &= 129 \text{ mg Gd/kg-day} \end{aligned}$$

The subchronic p-RfD for gadolinium was derived using the POD (HED) and a composite uncertainty factor (UF_C) of 3,000 (reflecting an interspecies uncertainty factor [UF_A] of 3, an intraspecies uncertainty factor [UF_H] of 10, a LOAEL-to-NOAEL uncertainty factor [UF_L] of 10 for use of a LOAEL as the POD, and a database uncertainty factor [UF_D] of 10):

$$\begin{aligned} \textbf{Screening Subchronic p-RfD for Soluble Gadolinium} &= \text{POD (HED)} \div UF_C \\ &= 129 \text{ mg Gd/kg-day} \div 3{,}000 \\ &= \mathbf{4 \times 10^{-2} \text{ mg Gd/kg-day}} \end{aligned}$$

Table A-1. Uncertainty Factors for the Subchronic p-RfD for Gadolinium and Soluble Salts

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between animals and humans following oral gadolinium exposure. The toxicokinetic uncertainty is accounted for by calculation of an HED through application of a DAF as outlined in the U.S. EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_D	10	A UF_D of 10 is applied to account for the limited oral toxicity database for gadolinium, which consists of a published subchronic-duration dietary study in rats (Haley et al., 1961) and a 28-d rat gavage study available only as an abstract (Ogawa et al., 1992). No studies have been identified on the reproductive and developmental effects of gadolinium. Furthermore, no studies appear to have been conducted on potential neurotoxicity and neurodevelopmental effects. Such studies might be toxicologically relevant because gadolinium has been shown to disrupt calcium homeostasis, which can be a potential mechanism for neurotoxicity.
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of gadolinium in humans.
UF_L	10	A UF_L of 10 is applied because the POD is a LOAEL.
UF_S	1	A UF_S of 1 is applied because a subchronic-duration study is selected as the principal study.
UF_C	3,000	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

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

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

DERIVATION OF A SCREENING CHRONIC PROVISIONAL REFERENCE DOSE

A screening chronic p-RfD is not derived for soluble gadolinium. There are no studies of chronic exposure to any soluble gadolinium compound in any species, and the subchronic exposure study of gadolinium chloride by Haley et al. (1961) was not considered suitable for derivation of a screening chronic p-RfD. Toxicokinetic studies of gadolinium compounds indicate substantial deposition to the skeleton. To this point, Leggett et al. (2014) reported median molar concentrations of gadolinium and other lanthanides among a population of 68 adult Chinese men in a number of tissues based on data obtained by Chen et al. (2010). While the nature and magnitude of lanthanide exposure in this study was not well described, the highest gadolinium concentrations were observed in the rib and lung (14 nmol/kg fresh weight each), followed by thyroid and thymus (4.1 nmol/kg) (Leggett et al. (2014). The authors of this study indicated that the data were very uncertain due to potential errors in measuring tissue concentrations and the high variability observed in the measured concentrations. An earlier

study by Durbin et al., (1956) suggests that intramuscular administration of radioactive gadolinium oxides (chelated in a citrate solution to increase the speed of absorption) to rats results in deposition of approximately 45% of radioactivity in bone. Although long-term retention of gadolinium has not been studied, the elimination of lanthanides from bone has been observed to be extremely slow. For example, based on data obtained over 256 days, Durbin et al. (1956) estimated a half-life of 2.5 years for elimination of the closely related lanthanide europium from bone. In summary, the potential for prolonged retention of gadolinium in the body bolsters the uncertainty surrounding the extrapolation of the LOAEL observed in a subchronic-duration study to effects after chronic exposure. Consequently, no screening chronic p-RfD has been derived for soluble gadolinium.

APPENDIX B. DATA TABLES

Table B-1. Perinuclear Vacuolization and Coarse Granular Cytoplasm in Parenchymal Cells of the Liver[a]

Exposure Group (mg Gd/kg-day)	Male Rats Exhibiting Perinuclear Vacuolization and Coarse Granular Cytoplasm in Parenchymal Cells of the Liver (# positive/total)
0	ND
5.38	ND (reported as "effects not regularly observed")
53.8	ND (reported as "effects not regularly observed")
538	6/6

[a]Haley et al. (1961).

Gd = gadolinium; ND = no data.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

Benchmark dose (BMD) modeling was not performed for this assessment.

APPENDIX D. REFERENCES

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