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Toxicology Assessment for Department of Defense Strategic Environmental Research and Development Program (SERDP) Project WP-2518: Environmentally Sustainable Gasless Delay Compositions for Fuzes, March 2015–April 2018

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14. ABSTRACT
A Toxicology Assessment was prepared in support of a gasless delay fuze formulation that eliminates barium chromate, potassium perchlorate, and lead chromate from the mixture. The report addresses the human health and environmental effects of compounds of manganese, silicon, iron, tungsten, titanium, zirconium, tin, cobalt, boron, aluminum, antimony, strontium, molybdenum as well as polytetrafluoroethylene, While some of the compounds being considered are toxic via inhalation, the combustion products of the proposed fuze combination are not released to the atmosphere and therefore pose no inhalation threat and do not represent a human health or environmental hazard in this configuration.

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1 Summary

1.1 Overview

Research, development, testing, training, and use of substances potentially less hazardous to human health and the environment are vital to the readiness of the U.S. Army. Safeguarding the health of Soldiers, civilians, and the environment requires an assessment of alternative substances before they are fielded. Continuous assessments begun early in the research, development, test, and evaluation (RDT&E) process can save significant time and effort not only during RDT&E but over the life cycle of the items developed, as well. Residues of pyrotechnics, propellants, explosives and incendiaries used in mission-essential activities have been found in soil, air, surface and groundwater samples. Remediation of contaminated areas has cost the Department of Defense (DOD) millions of dollars and can interfere with training activities.

1.2 Purpose

Pyrotechnic delay compositions are used by the U.S. Military in a variety of munitions, especially in fuzes for hand grenades. Thousands of these items are used on military training ranges in the U.S. each year, creating a significant range contamination hazard with potential subsequent training disruptions. The use of toxic materials (barium, lead, and chromium salts and perchlorates) in these delay compositions increases the costs of complying with environmental safety and occupational health (ESOH) regulations in manufacturing. The goal of this project is to develop a replacement for the current delay compositions that would reduce or eliminate the toxic materials in the current formulations, and provide operational and cost advantages, as well as human health and environmental benefits.

1.3 Conclusions

In its design configuration, the proposed formulation represents a low hazard to both human health and the environment. The gasless delay fuze is intended to ignite the munition's main charge after a period of delay to permit deployment of the munition (e.g., fragmentation or smoke grenade) without co-production of gaseous reaction products that would cause the container to rupture and release materials to the environment. Some of the reaction products produced represent inhalation hazards, but these are not expected to be significant since there is no environmental release. Exposure to the materials of the formulation is limited to manufacture and post-ignition degradation. As none of the materials pose a significant dermal contact hazard, occupational exposures are anticipated to be of low hazard. The munitions fragments that remain after the device's use are likely to be released to the environment only through weathering. The human health and environmental effects of these released compounds are expected to be minimal, as their groundwater transport potential is limited, the ultimate compounds are ubiquitous in the environment, and the chemicals released are generally considered low in toxicity. Although there are some data gaps across the board for these substances, the conditions of use (i.e., no significant inhalation exposure) for this item do not mandate that these gaps be filled at this time. Should these substances be present in other formulations where significant exposure, especially by inhalation, is a possibility, additional data

collection would be desired.

This project is somewhat atypical since all of the constituent compounds are inorganic substances that have not undergone the number of deliberate/systematic toxicity testing studies that newly-developed organic compounds (e.g., pharmaceutical and agricultural chemicals) receive. Toxicity evaluation of inorganic chemicals is further complicated by the tendency of these substances to undergo oxidation-reduction reactions, both in the environment and within biological organisms. In some cases, product literature (often the only available source of information) may assert that a substance has a defined toxicological endpoint but fail to provide supporting data, and such data cannot be found by regular literature search. In some cases, the only information available was anecdotal and did not indicate the boundaries of the responses.

Quantitative Structure-Activity Relationship (QSAR) modeling cannot currently be carried out on inorganic materials.

1.4 Recommendations

Due to the nature of the device in which this delay formulation is to be deployed, no human inhalation exposure is expected since “no” gases are released from the device. The principal means of release to the environment is expected to be by degradation of the expended delay element through weathering. As all of the combustion products are minerals common to soils and are of low toxicity, there are no recommendations for additional toxicity data collection at this time. Should this formulation be used in applications where release to the environment is anticipated, a reassessment of the conclusions of this investigation would be required.

2 References

See Appendix A for list of the references cited in this report.

3 Authority

Funding for this work was provided under Military Interdepartmental Purchase Request No. W74RDV50133546. This Toxicology Assessment addresses, in part, the ESOH requirements outlined in the following—

- Army Regulation (AR) 200–1, Environmental Protection and Enhancement, 2007;
- AR 40–5, Preventive Medicine, 2007;
- AR 70–1, Army Acquisition Policy, 2018;
- Department of Defense Directive 4715.1E, Environment, Safety, and Occupational Health (ESOH), 2005; Change 1, 2018; and
- Army Environmental Requirement and Technology Assessment Requirement PP-3-02-05, Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces, 2012.

The Sponsor is the Strategic Environmental Research and Development Program (SERDP). The Principal Investigators are Drs. Jay Poret and Anthony Shaw of the U.S. Army Armament Research, Development and Engineering Center (ARDEC), Picatinny Arsenal, New Jersey.

4 Background

Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and groundwater. If applied after an item has been fielded, these assessments can reveal the existence of adverse environmental and human health effects that must be addressed, often at substantial cost. It is more efficient to begin the assessment of exposure, effects, and environmental transport of military-related compounds/ substances early in the RDT&E process to avoid unnecessary costs, conserve physical resources, and sustain the health of U.S. Forces and others potentially exposed.

In an effort to support this preventive approach, the U.S. Army Public Health Center (APHC) has been tasked with creating a phased process to identify ESOH effects impacting readiness, training, and development costs. This report represents the status of information available for this work unit as of the date of publication.

5 Statement of the Problem

Current delay fuze compositions are based upon tungsten, manganese, boron, or zirconium-nickel alloys to which barium chromate, potassium perchlorate, or lead chromate have been added. The barium chromate, potassium perchlorate and lead chromate pose an unacceptable human health and environmental hazard. Three delay formulations commonly used in U.S. Army pyrotechnic and explosive devices (e.g., hand grenades) are as follows:

- The tungsten delay is a 4-component mixture of tungsten, barium chromate ($BaCrO_4$), potassium perchlorate ($KClO_4$), and diatomaceous earth. Toxic components of this formulation are the barium, chromium(VI), and perchlorate anion, all of which pose both human health and environmental hazards.

- The second type of delay, the manganese delay, is a 3-component mixture of elemental manganese, barium chromate, and lead chromate ($PbCrO_4$). As noted previously, barium, and chromium(VI), are both toxicity hazards, and this formulation also contains lead, an extreme human and environmental toxicant.

- The third type of delay, the zirconium-nickel delay, is a three-component mixture of a zirconium-nickel alloy, barium chromate, and potassium perchlorate. Nickel compounds are extremely toxic to humans and the environment. As above, barium, chromium(VI), and perchlorate are also present.

Combustion of these delays results in the production of components that are released to the environment upon weathering of the munition residue. Release of these toxic metals has an adverse effect on both human health and the environment; the development of more benign alternatives is desired.

6 Methods

In order to determine the human health and environmental impact of compounds employed in these formulations, it is necessary to identify each compound correctly and to determine its physical, chemical, and toxicological properties. The primary means of identification employed for each compound in this program is its Chemical Abstracts Service Registry Number (CAS RN) (Table 1). While all compounds do not necessarily have a single CAS RN, the CAS RN is an unambiguous means of accessing information about chemical substances. The CAS RN is readily used as a keyword for searching online databases and is often cross-referenced with both systematic and trivial (i.e., “common” or non-systematic) names for chemical substances. In some cases, synonyms and trade names are also used to identify structures.

Table 1. Formulation Components and Predicted Products

Chemical Substance	CAS Number
Manganese, elemental [Mn]	7439-96-5
Manganese oxide [MnO]	1344-43-0
Manganese dioxide [MnO_2)	1313-13-9
Manganese(II,III) oxide [Mn_3O_4]	1317-35-7
Manganese tungstate [$MnWO_4$]	14177-46-9
Silicon, elemental [Si]	7440-21-3
Silica [SiO_2]	7631-86-9
Bismuth oxide[Bi_2O_3]	1304-76-3
Red iron oxide [Fe_2O_3]	1332-37-2
Black iron oxide [Fe_3O_4]	1309-38-2
Tungsten [W]	7440-33-7
Tungsten oxide [WO_3]	1314-35-8
Titanium [Ti]	7440-32-6
Titanium dioxide [TiO_2]	13463-67-7
Titanium hydride [TiH_2]	7704-98-5
Titanium boride [TiB_2]	12045-63-5
Titanium carbide [TiC]	12070-08-5
Potassium nitrate [KNO_3]	7757-79-1
Zirconium [Zr]	7440-67-7
Polytetrafluoroethylene [PTFE]	9002-84-0
Tin [Sn]	7440-31-5
Tin oxide [SnO]	21651-19-4
Tin dioxide [SnO_2]	18282-10-5
Cobalt [Co]	7440-48-4
Cobalt oxide [CoO]	1307-96-6
Cobalt(II,III) oxide [Co_3O_4]	1308-06-1
Boron oxide [B_2O_3]	1303-86-2
Antimony(III)oxide [Sb_2O_3]	1309-64-4
Aluminum [Al]	7429-90-5
Aluminum oxide [Al_2O_3]	1344-28-1
Aluminum silicate [Al_2SiO_5]	1344-00-9

Chemical Substance	CAS Number
Ammonium dihydrogen phosphate	7722-76-1
Strontium molybdate [$SrMoO_4$]	13470-04-7
Strontium oxide [SrO]	1314-11-0
Strontium silicate [$SrSiO_3$]	13451-00-8, 12712-63-9
Strontium aluminate [$SrAl_2O_3$]	12004-37-4
Molybdenum silicides [Mo_5Si_3],[$MoSi_2$]	12136-78-6

In this report, the investigators requested an expansion of the list of compounds under consideration to include the various combustion products that might be formed from the initial components.

The properties necessary to assess fate and transport in the environment include—

- Molecular weight (MW).
- Boiling point (bp).
- Octanol-water partition coefficient (log K_{OW}).
- Organic carbon partition coefficient (log K_{OC}).
- Water solubility
- Henry's law constant (K_H).
- Vapor pressure (vp).

Basic physical and chemical properties are usually determined by consulting tertiary sources when such information is available.

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity and carcinogenicity; and mode(s) and mechanisms of toxicity. Toxicological information is derived directly from primary sources whenever possible.

Sources used in this search included *The Merck Index* (O'Neil 2006, Budavari 1996); the U.S. National Library of Medicine's Toxicology Data Network (TOXNET®), providing access to information from the National Institutes of Health and the U.S. Environmental Protection Agency (EPA); the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR); the EPA ECOTOXicology Database System (ECOTOX); and the Defense Technical Information Center (DTIC®). Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health

Organization (WHO), the National Center for Biotechnology Information, and the International Agency for Research on Cancer (IARC).

Primary references are identified and retrieved using PubMed® and the EBSCOhost® Research Databases. TOXNET provides links to a suite of individual databases including ChemID*plus*® (chemical structures, registration numbers, and links to other sites providing physical chemical properties of the compound), the Hazardous Substances Data Bank (HSDB®), TOXLINE (references to literature on biochemical, pharmacological, physiological and toxicological effects of drugs and other chemicals), the Developmental and Reproductive Toxicology database, the Comparative Toxicogenomics Database, the Integrated Risk Information System (IRIS), and the Animal Testing Alternatives database, as well as several others, including the archived databases for the Chemical Carcinogenesis Research Information System (CCRIS), the Carcinogenic Potency Database (CPDB), and the GENE-TOX genetic toxicity database. Commercial suppliers may provide results of in-house research that do not appear in the open literature.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general categories of risk (i.e., low, moderate, or high) using criteria modified from Howe et al. (2006). Table 2 describes the criteria used in the categorization; the relative proportions of each substance were also factored into the final assessment. Appendix B provides the Globally Harmonized System (GHS) classifications, as per the Occupational Safety and Health Administration (OSHA) (Federal Register 2012), for many of these compounds.

Table 2. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity[1]

	Low	Moderate	High
PERSISTENCE	Readily biodegrades (<28 days)	Degradation ½ life: water <40 days, soil <120 days	Degradation ½ life: water >40 days soil > 120 days
TRANSPORT	Water sol. <10 mg/L log K_{OC} >2.0	Water sol. 10–1000 mg/L log K_{OC} 2.0–1.0	Water sol. >1000 mg/L log Koc <1.0
BIOACCUMULATION	log K_{OW} <3.0	log K_{OW} 3.0–4.5	log K_{OW} >4.5
TOXICITY	No evidence of carcinogenicity/ mutagenicity; Subchronic LOAEL >200 mg/kg-day	Mixed evidence for carcinogenicity/mutagenicity (B2, 2); Subchronic LOAEL 5–200 mg/kg-day	Positive corroborative evidence for carcinogenicity/ mutagenicity; LOAEL <5 mg/kg-day
ECOTOXICITY	Acute LC_{50}/LD_{50} >1 mg/L or 1500 mg/kg; Subchronic EC_{50} >100 µg/L or LOAEL >100 mg/kg-day	Acute LC_{50}/LD_{50} 1–0.1 mg/L or 1500–150 mg/kg; Subchronic EC_{50} 100–10 µg/L or LOAEL 10–100 mg/kg-day	Acute LC_{50}/LD_{50}<100 µg/L or <150 mg/kg; Subchronic LOAEL <10 mg/kg-day

Legend:
LC50 = concentration expected to result in 50% lethality to a population of test animals
LOAEL = lowest-observed adverse effect level
mg/kg-day = milligrams per kilogram per day
mg/L = milligrams per liter
µg/L = micrograms per liter

Note:
[1] Modified from Howe et al. 2006

Because several of the compounds addressed in this report are related to one another due to the nature of the oxidation/combustion process, it was decided to treat each of these families of starting metal and daughter products together so as to better portray their relationship to one another. In many cases, the exact speciation of the metal ion responsible for a particular toxicological effect is unclear, as metals may undergo oxidation-reduction processes within biological systems. Accordingly, the toxic effect may not be attributable at a greater level of detail than the particular metallic element, with the valence of the element being unclear; hence, they tend to be assessed together under the parent element.

7 Results

7.1 Physical Properties

Table 3 summarizes the physical and chemical properties of the compounds. “ND” indicates no data were found, and “n/a” indicates the property named is not applicable to the substance being described. For example, if the compound is a nonvolatile solid or an inorganic salt, the vapor pressure, K_{OW}, K_{OC}, and the Henry’s Law constant (K_H) are typically negligible.

Table 3. Physical Properties

Compound (Chemical formula)	Molar Mass (g/mol)	Melting Point (ºC)	Boiling Point (ºC)	Aqueous solubility (mg/L) @ 25ºC	log K_{ow}	log K_{oc}	Henry's Law Constant (atm-m^3/mol) @ 25ºC	Vapor Pressure mmHg @ 25°C
Mn	54.94[a]	1244[a]	2095[a]	Insoluble[a]	n/a	n/a	n/a	n/a
MnO_2	86.94[a]	530[a] (dec)	ND	Insoluble[a]	n/a	n/a	n/a	n/a
MnO	70.94[a]	1650[a]	ND	Insoluble[a]	n/a	n/a	n/a	n/a
Mn_3O_4	228.81[a]	1564[a]	ND	Insoluble[a]	n/a	n/a	n/a	n/a
SiO_2	60.08[a]	1720[b]	2230[b]	Insoluble[a]	n/a	n/a	n/a	n/a
Si	28.09[c]	1412[a]	2680[a]	Insoluble[a]	n/a	n/a	n/a	n/a
Bi_2O_3	465.96[e]	817[a]	1890[a]	Insoluble[a]	n/a	n/a	n/a	n/a
Fe_2O_3	159.69[a]	1462[a] (dec)	ND	Insoluble[a]	n/a	n/a	n/a	n/a
Fe_3O_4	231.54[a]	1597[a]	ND	Insoluble[a]	n/a	n/a	n/a	n/a
W	183.85[a]	3410[a]	5900[a]	Insoluble[a]	n/a	n/a	n/a	n/a
Ti	47.90[a]	1668[a]	3278[a]	Insoluble[a]	n/a	n/a	n/a	n/a
TiH_2	49.88[a]	450[a]	n/a	Reactive	n/a	n/a	n/a	n/a
KNO_3	101.10[a]	337[a]	400[a] (dec)	3.8E+05[a]	n/a	n/a	n/a	n/a
Zr	91.22[d]	1857[d]	3577[d]	Insoluble[d]	n/a	n/a	n/a	n/a
PTFE	Variable	325[f] (gels)	500[f] (dec)	n/a	n/a	n/a	n/a	n/a
TiO_2	79.87[d]	1857[d]	ND	Insoluble[b]	n/a	n/a	n/a	n/a
TiB_2	69.5[s]	2900[i]	ND	Insoluble[i]	n/a	n/a	n/a	n/a
TiC_2	59.88[h]	3140[h]	4820[h]	Insoluble[h]	n/a	n/a	n/a	n/a
WO_3	231.85[j]	3410[k]	5660[k]	Insoluble[j]	n/a	n/a	n/a	n/a
$MnWO_4$	302.77[n]	ND	ND	Insoluble[n]	n/a	n/a	n/a	n/a
Sn	118.71[a]	231.89[a]	2507[a]	Insoluble	n/a	n/a	n/a	n/a
SnO_2	150.71[a]	1630[a]	1800–1900 (sublimes)[a]	Insoluble[a]	n/a	n/a	n/a	n/a
Co	58.93[l]	1495[l]	2927[l]	Insoluble[a]	n/a	n/a	n/a	n/a
CoO	74.93[a]	1935[a]	ND	Insoluble[a]	n/a	n/a	n/a	n/a
Co_3O_4	240.80[a]	ND	ND	Insoluble[a]	n/a	n/a	n/a	n/a

Compound (Chemical formula)	Molar Mass (g/mol)	Melting Point (ºC)	Boiling Point (ºC)	Aqueous solubility (mg/L) @ 25ºC	log K_{ow}	log K_{oc}	Henry's Law Constant (atm-m^3/mol) @ 25ºC	Vapor Pressure mmHg @ 25°C
Sb_2O_3	291.52[a]	655[a]	1425[a] (dec)	Slightly soluble[a]	n/a	n/a	n/a	n/a
B_2O_3	69.62[o]	450.0[p] (crystalline form)	1500[o] (crystalline form)	27,700[o]	ND	ND	ND	n/a
Al	26.98[a]	660[a]	2518[a]	Insoluble[a]	n/a	n/a	n/a	n/a
Al_2O_3	101.96[p]	2030[q]	2977[q]	Insoluble[q]	n/a	n/a	n/a	n/a
$[NH_4][H_2PO_4]$	115.03[a]	190[a] (dec)	n/a	3.7E+05[a]	n/a	n/a	n/a	n/a
$Al_4O_{12}Si_3$	384.17[r]	1810[s]	ND	Insoluble[s]	n/a	n/a	n/a	n/a
$SrMoO_4$	247.56[v]	1040[b]	Dec	Nearly insoluble	ND	ND	ND	n/a
$SrAl_2O_4$	205.58[w]	ND	ND	ND	ND	ND	ND	ND
SrO	103.63[a]	2430[a]	n/a	0.0695@ 20°C[a]	n/a	n/a	n/a	n/a
$MoSi_2$	153.86[t]	1870[u]	n/a	Insoluble[u]	n/a	n/a	n/a	n/a

Legend:
dec = decomposes
n/a = not applicable
ND = no data

Key:
a = Dean 1992
b = NIOSH 2016
c = ChemID*plus* 2013a
d = O'Neil 2006
e = HSDB 2002a
f = HSDB 2002b
g = HSDB 2006c
h = ESPI 2015
i = Fisher Scientific 2015b
j = HSDB 2005e
k = Koutsospyros et al. 2006
l = HSDB 2006c
m = PubChem 2017b
n = ChemID*plus* 2017
o = PubChem 2017e
p = Budavari 1996
q = HSDB 2011b
r = PubChem 2017f
s = Sigma-Aldrich 2015a

t = PubChem2017g
u = ESPI 2007
v = PubChem 2017h
w = PubChem 2017i

7.2 Compound Summaries

Table 4 summaries the mammalian toxicity data. Tables 5 and 6 present the assessments of human health and environmental toxicity, respectively, for each of the formula components. Each characterization is generally based on the criteria in Table 2. The final risk characterization also incorporates an assessment of the uncertainty associated with available data, the amount of each compound present in the formulation, and the nature of potential exposure associated with use of the end item.

Table 4. Toxicity Data

Compound (Chemical formula)	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-day)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Genotoxicity	Carcinogenicity
Mn	225[a] (rats, gavage)	4.4[a] (mice)	ND	Negative[b]	ND	Negative[c]	Negative[b]
MnO_2	ND	ND	ND	Negative[c]	Negative[a]	Negative[c]	Negative[c]
MnO	ND	ND	ND	ND	ND	ND	Negative[d]
Mn_3O_4	ND	ND	ND	ND	ND	ND	ND
SiO_2	>5000[c]	ND	>200[d]	Negative[e]	Negative[e]	Negative[d]	Negative[d]
Si	3160[e] (rat)	ND	ND	Irritant[e]	Irritant[e]	Negtive[e]	Negative[e]
Bi_2O_3	ND	ND	ND	ND	ND	Limited evidence[e]	ND
Fe_2O_3	>10,000[f]	ND	ND	ND	ND	Negative[f]	Negative[f]
Fe_3O_4	500[g]	ND	Irritant[g]	Irritant[g]	ND	ND	ND
W	ND	ND	ND	Irritant[h]	Irritant[h]	ND	Negative[i]
Ti	ND	ND	ND	ND	ND	ND	Negative [j]
TiH_2	ND	ND	ND	ND	ND	ND	ND
KNO_3	3750[k] (rat) 1901[k] (rabbit)	ND	Irritant[k]	Irritant[k]	Irritant[k]	Negative[k]	Negative[k]
Zr	ND	ND	ND	ND	ND	ND	ND
PTFE	ND	ND	ND	ND	ND	Negative[l]	Negative[l]
TiO_2	ND	ND	ND	ND	ND	ND	ND
TiB_2	ND	ND	ND	ND	ND	ND	Negative[k]
TiC_2	ND	ND	ND	ND	ND	ND	ND

Compound (Chemical formula)	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-day)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Genotoxicity	Carcinogenicity
WO_3	3960[m]	ND	ND	100–1000 mg/kg[m]	Irritant[m]	ND	Negative[i]
$MnWO_4$	ND	ND	ND	ND	ND	ND	ND
Sn	ND	ND	ND	ND	Irritant[n]	ND	Possible with embedded fragments
SnO_2	20,000[o]	ND	ND	ND	ND	ND	ND
Co	ND	ND	ND	ND	ND	ND	ND
CoO	ND	ND	ND	ND	ND	ND	ND
Co_3O_4	ND	ND	ND	ND	ND	ND	ND
Sb_2O_3	>34,600[p]	ND	ND	Irritant[p]	Irritant[p]	Negative [p]	Negative[p]
B_2O_3	3163[q] (mice)	ND	ND	Irritant[q]	Irritant[q]	Negative[r]	Negative in humans[r]
Al	ND	ND	ND	Negative[q]	Negative[q]	ND	ND
Al_2O_3	>5000[s]	ND	ND	Negative	Irritant[s]	Negative	Negative
$[NH_4][H_2PO_4]$	ND	ND	ND	Irritant in dry form[r]	Irritant[r]	ND	ND
$Al_4O_{12}Si_3$	ND	ND	>0.002[t]	ND	Mild irritant[t]	Negative[t]	Negative in humans[t]
SrMoO4	ND	ND	ND	Irritant[u]	Irritant[u]	ND	ND
$SrAl_2O_4$	ND	ND	ND	ND	ND	ND	ND
SrO	ND	ND	ND	ND	ND	ND	ND
$MoSi_2$	ND	ND	Irritant	Irritant[u]	Irritant[u]	ND	ND

Legend:
ND = No data

Key:
a = Moreno et al. 2009
b = HSDB 2008a
c = ATSDR 2012
d = HSDB 2005a
e = HSDB 2002a
f = HSDB 2012a
g = HSDB 2005b
h = HSDB 2005c
i = ATSDR 2005a
j = HSDB 2003a
k =Sigma-Aldrich 2014
l = HSDB 2002b
m = HSDB 2005e
n = HSDB 2005f

o = PubChem 2017a
p = HSDB 2013
q = ATSDR 2008
r = Fisher Scientific 2012
s = HSDB 2011b
t = Sigma-Aldrich 2015a
u = Sigma-Aldrich 2016

Table 5. Toxicity Assessment

Compound (Chemical formula)	Oral	Inhalation	Dermal	Ocular	Carcino-genicity	Comments
Mn	Low	Mod	Low	Low	Low	Inhalation may cause metal fume fever after repeated exposures.
MnO_2	Low	Mod	Low	Low	Low	Parkinsonism-like neurological symptoms from overdose
Mn_3O_4	Low	Low	Low	Low	Low	
MnO_2	Low	Low	Low	Low	Low	Low solubility limits bioavailability
SiO_2	Low	Low	Low	Low	Low	
Si	Low	Low	Low	Low	Low	
Bi_2O_3	Low	Low	Low	Low	Low	
Fe_2O_3	Low	Low	Low	Low	Low	
Fe_3O_4	Mod	Low	Mod	Mod	Low	
W	Low	Low	Mod	Mod	Low	
Ti	Low	Low	Low	Low	Low	
TiH_2	Low	Mod	Mod	Mod	Unk	
KNO_3	Low	Low	Low	Low	Low	Methemoglobinemia most readily expressed clinical sign
Zr	Low	Low	Low	Low	Low	
PTFE	Low	Low	Low	Low	Low	Combustion and pyrolysis products toxic
TiO_2	Low	Low	Low	Low	Low	
TiB_2	Low	Low	Low	Low	Low	
TiC_2	Low	Low	Low	Low	Low	
WO_3	Low	Low	Low	Low	Low	OccHealth hazard
$MnWO_4$	Low	Low	Low	Low	Low	
Sn	Low	Low	Low	Low	Low	
SnO_2	Low	Low	Low	Low	Low	

Compound (Chemical formula)	Oral	Inhalation	Dermal	Ocular	Carcino-genicity	Comments
Co	Low	Low	Low	Low	Low	
CoO	Low	Low	Low	Low	Low	
Co_3O_4	Low	Low	Low	Low	Low	
Sb_2O_3	Low	Low	Mod	Mod	Low	
B_2O_3	Low	Low	Mod	Mod	Low	
Al	Low	Mod	Low	Low	Low	
Al_2O_3	Low	Low	Low	Low	Low	
$[NH_4][H_2PO_4]$	Low	Low	Low	Mod	Low	
$Al_4O_{12}Si_3$	Low	Mod	Low	Low	Low	
$SrMoO_4$	Mod	Mod	Mod	Mod	Low	
$SrAl_2O_4$	Low	Low	Low	Low	Low	
SrO	Low	Low	Low	Low	Low	
$MoSi_2$	Low	Low	Low	Low	Low	

Legend:
Unk = unknown

Table 6. Ecotoxicity Assessment

Compound (Chemical formula)	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
Mn	Low	Low	Low	Low	Unk	
MnO_2	Low	Low	Low	Low	Low	Low solubility limits bioavailability
MnO	Low	Low	Low	Low	Unk	
Mn_3O_4	Low	Low	Low	Low	Unk	
SiO_2	Low	Low	Low	Low	Unk	
Si	Low	Low	Low	Low	Unk	
Bi_2O_3	Low	Low	Low	Low	Low	
Fe_2O_3	Low	Low	Low	Low	Low	
Fe_3O_4	Low	Low	Low	Mod	Unk	
W	Low	Low	Low	Low	Unk	
Ti	Low	Low	Low	Low	Low	
TiH_2	Low	Unk	Unk	Low	Unk	Will react in water to produce H_2 gas and Ti(II) ions
KNO_3	Low	Low	Low	Low	Unk	KNO_3 is a component of fertilizers and a necessary plant nutrient.
Zr	Low	Low	Low	Low	Low	
PTFE	Low	Low	Low	Low	Low	
TiO_2	Low	Low	Low	Low	Low	
TiB_2	Low	Low	Low	Low	Unk	
TiC_2	Low	Low	Low	Low	Low	

Compound (Chemical formula)	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
WO_3	Low	Unk	Mod	Low	Unk	
$MnWO_4$	Low	Unk	Low	Low	Unk	
Sn	Low	Low	Unk	Low	Unk	
SnO_2	Low	Unk	Unk	Low	Unk	
Co	Low	Unk	Mod	Low	Low	
Co_3O_4	Low	Unk	Mod	Low	Low	
Sb_2O_3	Low	Low	Low	Low	Unk	
B_2O_3	Low	Unk	Low	Low	Unk	Boron is an essential plant nutrient.
Al	Low	Low	Low	Low	Unk	Moderate toxicity toward shellfish
Al_2O_3	Low	Low	Low	Low	Unk	
$[NH_4][H_2PO_4]$	Low	Low	Low	Low	Unk	
$Al_4O_{12}Si_3$	Low	Unk	Unk	Low	Unk	
$SrMoO_4$	Unk	Unk	Unk	Mod	Unk	
$SrAl_2O_4$	Unk	Unk	Unk	Unk	Unk	
SrO	Unk	Unk	Unk	Unk	Unk	
$MoSi_2$	Unk	Unk	Unk	Unk	Unk	

Legend:
Unk = unknown

7.3 Manganese and its oxides: [Mn, MnO, Mn_3O_4 and MnO_2]

7.3.1 General Information

Manganese exists in valences of 0, 2, 3, and 4. In this section, the term manganese (or Mn) is used if its speciation is either unknown or immaterial; the valence of the element is identified when the effect discussed is peculiar to that valence species (i.e., Mn(0) Mn(II), Mn(III), or Mn(IV)). All manganese oxides have multiple synonyms; for example, MnO is variously known as manganese(II) oxide, manganese monoxide, manganese oxide, manganosite, and manganese protoxide.

Manganese is a widely distributed, abundant element. It is an essential dietary nutrient and serves as both a constituent of metalloenzymes and an enzyme activator, with daily adequate intakes determined to be 2.3 mg/day for adult males and 1.8 mg/day for adult females. In humans and animals, manganese plays a role in bone mineralization, protein and energy metabolism, metabolic regulation, cellular protection from damaging free radical species, and formation of glycosaminoglycans (ATSDR 2012).

Mn, which is highly reactive, does not occur in pure form in nature but rather as a component of several minerals. The pure metal (Mn(0)) is steel gray in color, lustrous, hard, and brittle. Four allotropic forms are known. Below 710 degrees Celsius (ºC), the α-form, a body-centered cubic crystal structure, is the most stable.

7.3.2 Toxicology Data

The most common and serious health effect resulting from manganese exposure is a neurological Parkinson-like illness known as “manganism.” Manganism most often results from inhalation of manganese dust in an occupational setting. Symptoms of manganism include tremors, difficulty walking, and facial muscle spasms. These symptoms are often preceded by other lesser symptoms, including irritability, aggressiveness, and hallucinations. Some studies suggest that manganese inhalation can also result in adverse cognitive effects, including difficulty concentrating and memory problems (ATSDR 2012).

Exposure to fumes may result in “metal fume fever” (dry throat, coughing, tight chest, dyspnea, rales, and flu-like fever), lower back pain, vomiting, malaise, fatigue, and kidney damage (O’Neil 2006).

Limited data suggest that inorganic manganese may undergo changes in its oxidation state within the body. Circumstantial support for this hypothesis comes from the observation that the oxidation state of manganese in several enzymes appears to be Mn(III) (Leach and Lilburn 1978, Utter 1976), while most manganese uptake from the environment is either Mn(II) or Mn(IV) (ATSDR 2012).

Divalent Mn(II) is about 2.5 to 3 times more toxic than Mn(III); the anion of a manganese salt influences the overall manganese toxicity. Inhalation of manganese compounds in aerosols or fine dust produces “metal fume fever” (HSDB 2008a, 2008b).

The influence of manganese oxidation states on manganese toxicity is not currently well understood. Results from animal studies indicate the solubility of manganese compounds can influence the bioavailability of manganese and subsequent delivery to critical toxicity targets such as the brain (ATSDR 2012).

The manganese oxidation state is reported to have an impact on clearance from the body and possibly neurotoxicity (Gibbons et al. 1976). When $^{54}MnCl_2$ was incubated with fresh cow or goat serum for 20 hours, binding of manganese species to transferrin and α2-macroglobulin could be determined. Mn(II) was found to not bind to purified transferrin *in vitro* in the absence of an oxidizing agent. In the presence of permanganate, Mn(III) was formed and chelated by transferrin at physiological pH. Manganese in the divalent state, either as free Mn(II) or bound to α2- macroglobulin, is removed from blood plasma very efficiently by the liver; however, the Mn(III)- transferrin complex is not. It is not clear how the oxidation state of manganese is related to its normal function in neural cells or how this role is altered in manganese toxicity (ATSDR 2012).

The central nervous system (CNS) is the primary target of manganese toxicity. Although it is known that manganese is a cellular toxicant that can impair transport systems, enzyme activities, and receptor functions, the principal manner in which manganese neurotoxicity occurs has not been clearly established (Aschner & Aschner 1991, Aschner et al. 2007).

High levels of manganese may increase anemia by interfering with iron absorption; iron deficiency may increase an individual’s susceptibility to manganese poisoning (National

Research Council (NRC) 1980). Increased neurological problems associated with manganese ingestion have been noted where magnesium levels are low. A high incidence of motor neuron disease was noted in Hohara, Japan, where significantly increased manganese content in local rice and a decreased concentration of magnesium in the drinking water were positively correlated with the incidence of motor neuron disease (r^2=0.99) (Iwami et al. 1994; ATSDR 2012).

7.3.2.1 Oral

The endpoints for toxicological effects from oral exposure to Mn salts are generally neurological effects rather than frank toxicity. The chronic oral LD_{50} in rats for exposure to inorganic manganese (Mn_3O_4) is 225 mg/kg-day (ATSDR 2012). Manganese salts are poorly absorbed from the gastrointestinal tract (HSDB 2005d).

Evidence for the development of neurological symptoms from drinking water or consuming food containing higher than average levels of manganese is very limited. Kondakis et al. (1989) reported drinking water containing elevated levels of manganese (1.8–2.3 mg/L) led to an increased presence of neurological signs in elderly individuals (average age 67) in two small Greek towns. However, there are significant limitations to this study, and the efficacy of orally-consumed manganese in causing neurological effects is not conclusive.

Iwami et al. (1994) studied the metal concentrations in rice, drinking water, and soils in Hohara, a small town on the Kii peninsula of Japan. This town reportedly had a high incidence of motor neuron disease. The researchers observed that a significantly increased manganese content in local rice and a decreased concentration of magnesium in drinking water were positively correlated with the incidence of motor neuron disease (r^2=0.99).

Manganese has also been associated with amyotrophic lateral sclerosis (ALS, or Lou Gehrig's Disease). In a human study, spinal cord samples from ALS patients were found to have higher manganese concentrations in the lateral fasiculus and anterior horn than in the posterior horn (Kihira et al. 1990). ALS patients exhibited a positive correlation between manganese and calcium spinal cord content, whereas controls exhibited a negative correlation. It was suggested that an imbalance between manganese and calcium in ALS patients plays a role in functional disability and neuronal death. There was also some indication from previous studies that an excess of manganese in drinking water may have caused this imbalance although data to support this were not presented. While this is suggestive of an association between manganese and ALS, it is equally plausible that ALS leads to an imbalance in magnesium-calcium metabolism (ATSDR 2012).

A number of studies conducted in children exposed to relatively high levels of manganese via drinking water or food suggest, but generally do not support, a cause-effect relationship between various neurological and behavioral disorders and manganese exposure. Effects observed included poor school performance; low scores on neurobehavioral tests (e.g., digit span, Santa Ana manual dexterity, digit symbol, Benton visual retention test, and pursuit aiming test); poor intellectual performance testing, working memory, and perceptual reasoning; increased oppositional behavior and hyperactivity; and Attention Deficit Hyperactivity Disorder (ADHD)(ATSDR 2012). Manganese intakes were correlated with manganese levels in hair. In

one study (Bouchard et al. 2011), predicted IQ scores for children with 1 and 216 µg manganese/L in tap water concentrations differed by 6.2 full-scale IQ points.

The most sensitive endpoint in the rat is a LOAEL for neurological effects of 13.9 mg/kg-day (Shukakidze et al. 2003), and 4.4 mg/kg-day (Moreno et al. 2009) in the mouse, both employing $MnCl_2$•4 H_2O.

Manganese and iron compete for absorption both in the gut and at the blood-brain barrier (BBB). An excess of one metal will affect the brain distribution of the other.

Manganese-mediated alterations in iron pharmacokinetics may, at least in part, underlie some of the observed adverse neurological effects associated with elevated manganese exposure. In a rat study, intestinal transfer of calcium ions and manganese ions was found to be competitive. High dietary intakes of phosphorous and calcium have also been demonstrated to depress manganese uptake in chicks (ATSDR 2012).

Most studies indicate that Mn compounds have low acute oral toxicity when provided in feed. In rats, daily doses of 1300 mg/kg-day for 14 days did not affect survival (National Toxicology Program (NTP) 1993). However, when exposure is by gavage, the measured LD_{50} values for 1–21 days of exposure range from 225 to 1082 mg Mn/kg-day in rats and mice (ATSDR 2012).

7.3.2.2 Inhalation

Inhalation is the primary route of concern for manganese exposure. Inhalation of manganese dust for a period of a few months causes pulmonary pneumonitis in manganese industrial workers.

Manganese inhalation can result in metal fume fever, the symptoms of which are fever, chills, nausea, vomiting, abdominal pain, respiratory difficulties, fatigue, joint pain, and muscle aches. Onset of metal fume fever is typically rapid, within 3 to 10 hours of exposure (HSDB 2008a, 2008b).

Inhalation of particulate manganese compounds such as MnO_2 or Mn_3O_4 can lead to inflammatory response in the lung. This is characterized by an infiltration of macrophages and leukocytes that phagocytize the deposited manganese particles. Damage to lung tissue is usually not extensive but may include local areas of edema. Symptoms include cough, bronchitis, pneumonitis, and minor reductions in lung function. Occasionally, pneumonia may result (ATSDR 2012).

Inhalation of manganese oxide dust particles of about 3 µm in diameter for a few months causes pulmonary pneumonitis in manganese industrial workers, characterized by onset of pneumonia, intense dyspnea (difficulty breathing), high body temperature, acute signs of lobar pneumonia, and hemorrhage in lung with little expectoration (HSDB 2008a, 2008b).

Thompson et al. (2011) reported that in normal rats 7 days after nasal instillation of a single dose of $^{54}MnCl_2$, the mean concentration of radiolabel in the olfactory bulb was about 9- to 41-fold higher than concentrations in the other brain regions. These results indicate 1) the olfactory

bulb is the principal site of accumulation for manganese absorbed and transported to the brain via the nasal route, and 2) distribution from the olfactory bulb to other brain regions may be restricted.

Mice exposed to MnO aerosols, then infected with airborne *Streptococcus pyrogenes*, showed greater mortality than controls. Maximum rates were determined from 2 hours of exposure. Toxic effects also indicated reduced initial clearance and subsequent enhanced growth of bacteria (Adkins et al. 1980).

7.3.2.3 Dermal

Elemental manganese is poorly absorbed dermally, and systemic toxicity from this route of exposure is not expected (HSDB 2008a). Dermal exposures may lead to dermal irritation and contact dermatitis (HSDB 2005b).

7.3.2.4 Ocular

Mn(0) dust and fumes are irritants to the eyes (HSDB 2008a).

Manganese poisoning affects the eyes by decreasing the movement of eyelids and eyes. Neither paresis (weakness) of eye muscles nor nystagmus (involuntary eye movement) occurs (HSDB 2008b).

7.3.2.5 Development and Reproduction

There is evidence to suggest that children exposed to high levels of manganese from environmental sources may exhibit a variety of adverse developmental effects, neurological in particular. Neurological effects in children exposed to excess levels of manganese in water (≥0.2 mg/L) include poor school performance, impaired cognitive function, abnormal performance on neurobehavioral tests, and increased oppositional behavior and hyperactivity (ATSDR 2012).

Hafeman et al. (2007) conducted a study of infant mortality in a Bangladesh community whose local drinking water supply was contaminated by high levels of manganese. The Health Effects of Arsenic Longitudinal Study was conducted on 11,749 participants 18–70 years of age living in Araihazar, Bangladesh. Eighty-four percent of infants were exposed, either directly or through maternal intake, to water manganese levels greater than 0.4 mg/L. Of the 3,837 children born to women who reported having drunk from the same well for most of their childbearing years, 335 died before reaching 1 year of age. Adjustment for water arsenic, indicators of social class, and other potential variables and confounders did not appreciably alter the results. The authors concluded that infant exposure to manganese was complex and that it was not possible to infer that the manganese was solely responsible for the high infant mortality documented in the study.

Impotence and loss of libido are common symptoms in male workers with clinically identifiable signs of manganism. Impaired fertility has been observed in male workers exposed for 1–19 years to manganese dust (0.97 mg/m^3) at levels that did not produce frank manganism. It is not possible to identify a threshold for these effects due to lack of dose-response data. Studies in laboratory animals have found exposure to high levels of manganese may adversely affect sperm quality, produce decreased testicular weights, and impair development of the male reproductive system (ATSDR 2012).

Manganese has not been found to adversely affect fertility in women (ATSDR 2012).

Manganese deficiency during gestation has demonstrated adverse effects on the central nervous system (CNS) of the developing fetus in experimental animals (HSDB 2005d).

There are few developmental or reproductive studies of manganese in laboratory animals. Dorman et al. (2005) conducted a study where female CD rats were exposed via inhalation to $MnSO_4$ at concentrations of 0.05, 0.5, or 1.0 mg Mn/m^3 for 6 hours/day, 7 days/week from 28 days prior to breeding through post-natal day (PND) 18. Despite increased manganese concentration in several maternal tissues, $MnSO_4$ exposure did not affect body weight gain, terminal PND 18 body weight, or organ weights in the dams. High-dose manganese exposure was associated with decreased brain weight in PND 14 pups, PND 19 female pups, and PND 45 male pups. High-dose exposure was also associated with decreased liver weight in PND 19 pups and PND 63 male pups. All other organ weights in pups were comparable to controls. Increased manganese concentrations were observed in several organs in pups from PND 1 through PND 45. Brain manganese concentrations in newborn rats were initially unaffected by the high-dose exposure that occurred *in utero.* However, by PND 14, increased brain manganese concentrations were observed in $MnSO_4$-exposed pups and remained approximately 2- to 3-fold higher than control animals through lactation. Newborn pups were exposed to higher than usual manganese concentrations in the milk; milk manganese concentrations were approximately 1.8- to 8-fold higher than controls.

Animal studies have failed to demonstrate teratogenic effects in animals from inhalation of Mn(0); however, Mn-deficiency during gestation has demonstrated adverse effects on the CNS of the developing fetus in experimental animals (HSDB 2008a).

7.3.2.6 Neurotoxicity

Inhalation of high levels of manganese results in the disease known as “manganism.” Initial symptoms include feelings of weakness or lethargy, followed by the development of other neurological signs, such as slow and clumsy gait, speech disturbances, a mask-like face, and tremors. These symptoms are similar to—but distinguishable from—Parkinson’s disease. In most cases, symptoms continue to manifest for many years post-exposure, even when the manganese source is no longer present (ATSDR 2012).

Chronic exposure to atmospheres containing from about 0.07 to 0.97 mg Mn/m^3 have been known to cause sub-clinical effects in chronically-exposed workers, including decreased performance on neurobehavioral tests, significantly poorer hand-eye coordination, hand steadiness, poor reaction time, poorer postural stability, and lower levels of cognitive flexibility (ATSDR 2012).

Neuropsychiatric symptoms were studied among formerly Mn(0)-exposed workers 14 years after cessation of exposure. The study was initiated in 1990 with a follow-up examination in 2004. A Brief Symptom Inventory (BSI) was administered, and the results were converted to T-scores based on a normative population. Cumulated Exposure Indices (CEI) were computed for each worker. Mean T-scores were significantly higher among former manganese workers on scales of Depression and Anxiety; mean T-scores of psychological distress increased with the

CEI tertiles, with significant associations for Somatization, Depression, Anxiety, and Hostility scales. These results suggest exposure to Mn may have lasting consequences on neuropsychiatric symptoms (Bouchard et al. 2007).

The principal manner in which manganese neurotoxicity occurs has not been clearly established (Aschner & Aschner 1991; Ashner et al. 2007).

7.3.2.7 Genotoxicity

Mutagenicity studies in both bacteria and mammalian cell lines are equivocal. The results of *in vitro* studies show that at least some chemical forms of manganese have mutagenic potential. However, since the results of *in vivo* studies in mammals are inconsistent, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds (ATSDR 2012).

7.3.2.8 Carcinogenicity

There is no evidence that manganese compounds are carcinogenic. The EPA IRIS classification for manganese is D, “not classifiable as to human carcinogenicity” (ATSDR 2012).

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

Manganese compounds have negligible vapor pressures but may exist in air as suspended particulate matter derived from industrial emissions or the erosion of soils. Manganese-containing particles are mainly removed from the atmosphere by gravitational settling (USEPA 1984, ATSDR 2012).

Transport and partitioning of manganese in water is controlled by the solubility of the specific chemical form present, which in turn is determined by pH, the oxidation-reduction potential, and the characteristics of the available anions. Mn(II) predominates in most waters (pH 4–7), but all four oxidation states are possible. The principal anion associated with Mn(II) in water is usually carbonate, and the concentration of manganese is limited by the relatively low solubility of manganese carbonate. Under oxidizing conditions, Mn(III) and Mn(IV) may be formed (ATSDR 2012).

The tendency of soluble manganese compounds to adsorb to soils depends upon the anion exchange capacity and organic content of the soil (ATSDR 2012). Baes and Sharp (1983, cited in ATSDR 2012) noted that soil adsorption constants span five orders of magnitude, ranging from 0.2 to 10,000 mg/L, increasing as a function of the organic content and the ion exchange capacity of the soil. In some cases, adsorption of manganese to soils may not be readily reversible.

Manganese in water may be significantly bioconcentrated at lower trophic levels. Thompson et al. (1972) estimated the bioconcentration factors (BCFs) of manganese were 10,000–20,000 for marine and freshwater plants, 10,000–40,000 for invertebrates, and 100–600 for fish.

7.3.2.9.2 Ecotoxicity

Manganese can induce iron deficiency in some algae, notably blue-green algae, and this

deficiency can lead to inhibition of chlorophyll synthesis. The mechanism is thought to be competition for an active site where iron is necessary for functional integrity. Filamentous green algae (*Ulothrix minuta* and *U. fimbriata*) common in streams receiving acid mine drainage showed significant growth reductions at 20 mg Mn/L (as $MnSO_4$), in 15-day tests; algae were unaffected by pH levels typical of contaminated streams (HSDB 2008b).

Little information is available regarding the chronic toxicity of manganese in ecosystems. Available data indicate that manganese is acutely toxic at relatively high aqueous concentrations in comparison to other trace metals, and its toxicity is affected by water hardness. In a study by Stubblefield et al. (1997), water hardness significantly affected manganese chronic toxicity, which decreased with increased water hardness. In an experiment conducted in early life stages of brown trout (*Salmo trutta*), decreased survival was the predominant effect noted at 30 mg $CaCO_3$-equivalent/L, while significant effects on growth were observed in both the 150 mg/L and 450 mg/L hardness experiments. Twenty-five percent (IC_{25}) inhibition values, based on combined endpoints (i.e., survival and body weight) were 4.67, 5.59, and 8.68 mg Mn/L at hardness levels of approximately equivalent to 30, 150, and 450 mg $CaCO_3$.

Mejia-Saavedra et al. (2005) studied the impact of manganese and DDT on the invertebrate *Daphnia magna* and the rotifer *Lecane quadridentata*. The LC_{50} for manganese alone was determined to be 17.7 µM (0.972 mg/L); the rotifer was much more resistant to the effects of both DDT and manganese.

A 96-hour EC_{50} of 31 mg manganese/L was determined for the common duckweed (*Lemna minor*), based upon growth (HSDB 2008b).

Lei et al. (2007) exposed cuttings of *Populus cathayana* to Hoagland's solution containing four different manganese concentrations (0, 0.1, 0.5 or 1 mM) in a greenhouse to characterize the physiological and biochemical basis of manganese resistance in woody plants. Two contrasting populations of *P. cathayana* from the wet and dry climate regions of western China were used in the study. The results showed that manganese treatments significantly decreased chlorophyll content and growth characteristics, including shoot height, basal diameter, biomass accumulation, and total leaf area, in the two populations. Manganese treatments also significantly increased the levels of abscisic acid, polyamines, and the free amino acids proline, histidine, and phenylalanine available for cellular signaling and heavy metal chelation. In addition, high manganese concentration also caused oxidative stress as indicated by the accumulation of hydrogen peroxide and malondialdehyde. The two populations responded to manganese stress in different ways. The wet climate plants accumulated more manganese in plant tissues, especially in leaves; and showed a lower tolerance index and a more pronounced decrease in growth and chlorophyll contents. Hence, the wet climate population was more susceptible to manganese stress than the dry climate population.

7.3.2.9.3 Degradation/Treatment

Manganese in water may undergo oxidation at high pH or oxidation-reduction potential and is also subject to microbial activity (ATSDR 2012),

Biotransformation of manganese compounds by microorganisms is an important process in

surface and ground waters. Insoluble Mn(III) and Mn(IV) compounds may be reduced by bacteria to soluble Mn(II) compound; the reverse process is also carried out by manganese-oxidizing bacteria, resulting in insoluble Mn(III) and Mn(IV) compounds (HSDB 2008b).

7.4 Silicon dioxide [Silica, SiO_2]

7.4.1 General Information

This section addresses both amorphous and crystalline silica characteristics. The formulas under consideration are believed to contain amorphous silica almost exclusively, but a small amount of crystalline silica may be present. Silicon dioxide occurs as transparent, tasteless crystals or as an amorphous powder. The amorphous powder form is commonly called diatomaceous earth, kieselguhr, or diatomite. Diatomaceous earth is formed from the skeletal remains of diatoms. Common uses include as a food additive (anti-caking agent), in cosmetics, as an absorbant, and other applications (HSDB 2005a).

Crystalline silicon dioxide ($cSiO_2$) is also known as silica or silicic anhydride. It is a frequently occurring solid component of most natural mineral dust and is the primary component of quartz sand. Crystalline SiO_2 is a transparent, tasteless substance that melts to a glass. $cSiO_2$ occurs in nature as agate, amethyst, chalcedony, cristobalite, flint, sand, quartz, and tridymite. SiO_2 has the lowest coefficient of thermal expansion by heat of any known substance. It is essentially insoluble in water or acids, with the exception of hydrofluoric and concentrated phosphoric acids (O'Neil 2006).

7.4.2 Toxicology Data

Toxicity of silica is dependent upon the occurrence of the crystalline structure. The toxicity characteristics of the amorphous and crystalline structures are significantly different. Processing amorphous silicon dioxide at high temperatures can result in crystalline forms that have different toxicity characteristics than those described in this section.

7.4.2.1 Oral

Amorphous silica is not toxic to rats at the limit dose of 5,000 mg/kg (ChemID*plus* 2013).

Rodent ingestion studies found that 95% of crystalline silica is not absorbed; it is excreted in the feces un-metabolized; 4% is excreted in urine, and 1% remains in tissues (HSDB 2005a).

7.4.2.2 Inhalation

The LC_{LO} for rats for crystalline silica is reported to be 2,190 mg/m^3 for a 4-hour exposure. The LC_{50} is reported to exceed 200 g/m^3-hour (ChemID*plus* 2013).

Potential symptoms of overexposure to crystalline silica as respirable dust (<5 µm diameter) are cough, dyspnea, wheezing, decreased pulmonary function, and pneumoconiosis (silicosis) (O'Neil 2006).

Because amorphous silica is less fibrogenic than crystalline silica, silicosis has rarely been observed after exposure to pure amorphous silica, but several cases have been reported. Repeated exposure to amorphous silica fumes causes "ferro-alloy disease" in humans,

characterized by recurrent fever over a period of 3–12 weeks and the appearance of x-ray markings similar to those seen with silicosis. These lesions do not progress, however, and in many cases, they revert spontaneously (HSDB 2005a).

Silicosis, lung cancer, and pulmonary tuberculosis are associated with occupational exposure to quartz dust. Statistically significant increases in deaths or cases of bronchitis, emphysema, chronic obstructive pulmonary disease, autoimmune related diseases (scleroderma, rheumatoid arthritis, systemic lupus erythematosis), and renal disease have been reported. Silicosis is the critical effect for hazard identification and risk assessment. There are sufficient epidemiological data to allow the risk of silicosis to be quantitatively estimated but not to permit accurate estimations of risks for other health effects (HSDB 2005a).

Quartz dust induces cellular inflammation *in vivo*. Short-term experimental studies of rats have found that intratracheal instillation of quartz particles leads to the formation of discrete silicotic nodules in rats, mice, and hamsters. Inhalation of aerosolized quartz particles impairs alveolar macrophage clearance functions and leads to progressive lesions and pneumonitis. Oxidative stress (formation of hydroxyl radicals, reactive oxygen species, or reactive nitrogen species) has been observed in rats after intratracheal instillation. Many experimental *in vitro* studies have found the surface characteristics of the crystalline silica particle influence its fibrogenic activity and a number of features related to its cytotoxicity. Long-term inhalation studies of rats and mice have shown that quartz particles produce cellular proliferation, nodule formation, suppressed immune functions, and alveolar proteinosis (HSDB 2005a).

Silica exposure has been found to have a number of extra-pulmonary effects, leading to the term “extrapulmonary silicosis,” which refers to the spread of lesions to the liver, spleen, kidneys, bone marrow, and extrathoracic lymph nodes (HSDB 2005a).

Occupational exposure to silica dust has been examined as a possible risk factor with respect to several systemic autoimmune diseases, including scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and some of the small vessel vasculitidies with renal involvement (e.g., Wegener granulomatosis). Experimental studies demonstrate that silica can act as an adjuvant to nonspecifically enhance the immune response. Since several autoimmune diseases appear to potentially be involved, silica may act to promote or accelerate disease development, requiring some other factor to break immune tolerance or initiate autoimmunity (Parks et al. 1999).

A nonsmoking animal feed worker developed severe irreversible airflow obstruction during a 2-year occupational exposure to organic matter, microorganisms, proteolytic enzymes, and both amorphous and synthetic silicates. Her pulmonary dysfunction failed to improve despite her removal from the workplace and treatment with bronchodilators and corticosteroids. Open lung biopsy demonstrated peribronchiolar inflammation, scarring within the small airways, and neolumen formation, all of which are findings consistent with bronchiolitis obliterans. Energy dispersive analysis of both the bronchoalveolar lavage fluid as well as the biopsy specimens revealed the presence of silicate particles, suggesting a potential link between the silica exposure and the pathologic findings. This case suggests bronchiolitis obliterans can occur as a consequence of occupational exposure in the animal feed industry. In addition, this entity should henceforth be considered when evaluating symptomatic patients with exposure to amorphous

and synthetic silicates (Spain et al. 1995).

Chronic inhalation of silica dusts of mixed or uncertain composition has resulted in observations of fibrosis in the lungs and lymph nodes. In rare studies, an increase in granulomatous tissue has been seen (HSDB 2005a).

In an inhalation study, rats were exposed, nose-only, to Ludox®, a commercial form of silica, at concentrations of 0, 10, 50, or 150 mg/m^3, 6 hours/day, 5 days/week for 4 weeks. Upon necropsy, no pulmonary effects were seen at the lowest concentration. However, at 50 and 150 mg/m^3, there was a concentration-related pulmonary response in the alveolar duct region characterized by silica-dust-laden alveolar macrophages, neutrophilic infiltration, and Type II pneumocyte hyperplasia. Tracheal and mediastinal lymph nodes were enlarged due to the macrophages and tissue hyperplasia (HSDB 2005a).

In a chronic study in rats where various nanoparticles were instilled intratracheally in doses up to 60 mg, amorphous silica induced few lung neoplasms, possibly because of its high solubility (Borm et al. 2006).

Inhaled amorphous silicon (mean particle size 0.02 µm) caused rapid death in rabbits exposed to 3,000 mg/m^3, but 100 mg/m^3 was better tolerated (HSDB 2005a).

7.4.2.3 Dermal

Fumed or precipitated hydrophobic amorphous silicas do not produce inflammation of the skin or mucous membranes (Lewinson et al. 1994). No data were found for crystalline silica.

7.4.2.4 Ocular

Amorphous silica is reported to be an ocular irritant (Sigma-Aldrich 2015a). Dusty particulates of either crystalline or amorphous silica are expected to be ocular irritants due to mechanical irritation.

7.2.4.5 Development and Reproduction

Reproductive or developmental toxicity from hydrophobic amorphous silica was not observed (Lewinson et al. 1994). No data were found for crystalline silica.

7.4.2.6 Genotoxicity

Quartz is negative in the standard bacterial genotoxicity assays (HSDB 2005a).

The comet assay under alkaline conditions (pH >13) was used to determine deoxyribonucleic acid (DNA) damage in cultured Chinese hamster lung fibroblasts (V79 cells) and human embryonic lung fibroblast cells (Hel299) exposed for a 3-hour period to either crystalline or amorphous silica at various concentrations. After amorphous silica treatment, tail length was increased relative to controls but not to the same extent as that induced by crystalline silica (Zhong et al.1997).

Several crystalline and amorphous silica dusts (two quartz of natural origin, one cristobalite of natural and two of biogenic origin, three amorphous diatomite earths, and one pyrogenic

amorphous silica) were studied in the Syrian hamster embryo (SHE) cell transformation assay. The results showed that some quartz and cristobalite dusts (crystalline) as well as the diatomaceous earths (amorphous), but not the pyrogenic amorphous silica, were cytotoxic and induced morphological transformation of SHE cells in a concentration-dependent manner. The ranking in cytotoxicity was different from that in transforming potency, suggesting two separate molecular mechanisms for the two effects. The cytotoxic and transforming potencies were different from one dust to another, even among the same structural silicas. The type of crystalline structure (quartz vs. cristobalite) and the crystalline vs. biogenic amorphous form did not correlate with the cytotoxic or transforming potency of silica dusts.

Comparison of cellular effects induced by original and surface-modified samples revealed that several surface functionalities modulate cytotoxic and transforming potencies. The cytotoxic effects appeared to be related to the distribution and abundance of silanol groups and to the presence of trace amounts of iron on the silica surface. Silica particles with fractured surfaces and/or iron-active sites, able to generate reactive oxygen species, induced SHE cell transformation. The results show that the activity of silica at the cellular level is sensitive to the composition and structure of surface functionalities and confirm that the biological response to silica is a surface-originated phenomenon. The authors concluded that these differing effects were moderated by the surface properties of the various silica particles, which varied even among the same structural type, and appear to be related to the ability of particles to induce reactive oxygen species (ROS). (Elias et al. 2000).

7.4.2.7 Carcinogenicity

Crystalline respirable silica, found primarily in industrial settings, is a known human carcinogen (O'Neil 2006).

There is inadequate evidence in humans for the carcinogenicity of amorphous silica, and inadequate evidence in animals for carcinogenicity of uncalcined diatomaceous earth. Amorphous silica is not classifiable as to its carcinogenicity to humans (HSDB 2005a).

No association was detected for mesothelioma with biogenic amorphous silica fibers in three community-based case control studies (HSDB 2005a).

Experimental studies in rats reported the occurrence of adenocarcinomas and squamous cell carcinomas after the inhalation or instillation of quartz. Pulmonary tumors were not observed in experiments with hamsters or mice (HSDB 2005a).

7.4.2.8 Ecotoxicology

7.4.2.8.1 Fate and Transport

Amorphous silica has a solubility of about 2.00 mmol/L (equal to 120 mg/mL) at pH 7 and 25°C (Vogelsberger et al. 1995); other forms of silica are less soluble.

7.4.2.8.2 Ecotoxicity

The 72-hour LC_{50} in carp is reported to be >10,000 mg/L (HSDB 2005a).

There have been several recent studies of ecotoxicity of silica particles to invertebrates and fish,

with special emphasis on nano-sized particles. Van Hoecke et al. (2008) found that while suspensions of commercial LUDOX® nanoparticles in the size range of 12.5 and 27.0 nm diameter were found to be toxic to green alga, with a NOEC of 4.6 mg/L and a LOEC of 10.0 mg/L. Bulk silica material was non-toxic at 1000 mg/L, the highest concentration tested. EC_{50} could not be determined because of the shape of the dose-response curve.

Canesi et al. (2010) investigated the impact of various nanomaterials, including nano-SiO_2, on the marine mussel *Mytilus galloprovincialis*. All nanoparticle suspensions induced significant lysosomal membrane destabilization in both hemocytes and the digestive gland, and increased the activity of catalase. A previous study by the same team found increases in oxyradical production and lysosomal enzyme release in hemocytes.

Lee et al. (2009) evaluated the effect of various nanomaterials, including nano-SiO_2, on *Daphnia magna* and *Chironomus riparius*. SiO_2 was found to not have a genotoxic effect and did not appear to affect DNA integrity but did cause an increase in mortality in both species.

7.4.2.8.3 Degradation/Treatment

Being inorganic in nature, silica in either form will not be readily degraded but will dissolve gradually depending upon the pH of the environment.

Due to lack of solubility, both amorphous and crystalline silica are expected to be readily removed by wastewater treatment processes, but amorphous silica may agglomerate and cause issues with the treatment equipment.

7.5 Silicon, elemental [Si]

7.5.1 General Information

Silicon may occur in an amorphous form or as black-to-grey, lustrous, needle-like crystals or octahedral platelets. The amorphous form is a dark brown powder (O'Neil 2006). Silicon produced at temperatures below 500°C by vapor deposition is generally amorphous; upon reheating to a somewhat higher temperature, crystallization will occur (HSDB 2011a). Numerous papers report ongoing evaluation of porous silicon in drug delivery applications (e.g., Kleps et al. 2009; Anglin et al. 2008).

7.5.2 Toxicology Data

7.5.2.1 Oral

The LD_{50} in rats for elemental silicon is reported to be 3,160 mg/kg (HSDB 2011a).

Cytotoxicity of mesoporous silicon microparticles was investigated on Caco-2 cells as a function of particle size fraction, particle concentration, and incubation time. Particles at the lower end of the size range (1.2–75 µm) were found to induce greater cytotoxicity, believed to be a result of mitochondrial disruption and adenosine triphosphate depletion and the production of reactive oxygen species (ROS). These events also caused an increase in cell apoptosis and consequent cell damage and cell death in a dose-dependent manner and as a function of particle size. Under the experimental conditions tested and at particle sizes >25 µm, the non-toxic threshold concentration for thermally hydrocarbonized and carbonized particles was <2 mg/mL, and for

thermally oxidized microparticles was <4 mg/mL (Santos et al. 2010).

7.5.2.2 Inhalation
Silicon dust causes irritation of the upper respiratory system and coughing. Silicon can be absorbed into the circulation after inhalation. Slight pulmonary epithelial lesions were found in rabbits after intratracheal instillation of silicon dust at 25 mg (HSDB 2011a).

7.5.2.3 Dermal
Silicon dust causes irritation of the skin (HSDB 2011a).

7.5.2.4 Ocular
Silicon dust causes irritation of the eyes (HSDB 2011a).

7.5.2.5 Development and Reproduction
No data were found.

7.5.2.6 Genotoxicity
Genotoxicity of silicon was investigated by soaking crystalline silicon in a complete culture medium for 60 days and conducting micronucleus tests utilizing Chinese hamster ovary (CHO) cells and the Ku80-deficient CHO mutant (xrs5) cells (DNA double-strand breaks repair efficiency). The intracellular concentrations of reactive oxygen/nitrogen species (ROS/RNS) on Si were determined. The results indicate that intracellular concentration of ROS and nitric oxide (NO) on Si is higher than that of the control group by about 38% and 12%, respectively. ROS/RNS species include superoxide anion, NO, and peroxynitrite, which can injure chromosomes and induce high cellular DNA double-strand breaks (Jiang et al. 2009).

7.5.2.7 Carcinogenesis
No data were found.

7.5.2.8 Ecotoxicology

7.5.2.8.1 Fate and Transport
Combustion of silicon may produce dusts of short duration, but their transport in the atmosphere is expected to be limited. Due to insolubility, silicon and its combustion products are not expected to bioaccumulate.

7.5.2.8.2 Ecotoxicity
No data were found.

7.5.2.8.3 Degradation/Treatment
Porous silicon nanoparticles are reported to be readily biodegradable (Hon et al. 2012).

7.6 Bismuth oxide [Bi_2O_3]

7.6.1 General Information
Bismuth oxide is a yellow powder with no acidic character (Cotton and Wilkinson 1972). Bismuth salts are used as medications for treatment of nausea, vomiting, and diarrhea (e.g., Pepto

Bismol™), in surgical paste for ileosotmies and colostomies, and as an adjunct in the treatment of ulcers. Bismuth salts were used historically for treatment of syphilis but cause kidney failure (HSDB 2002). Synonyms for bismuth oxide include bismuth yellow, dibismuth trioxide, bismuthous oxide, and oxo(oxobismuthanyloxy)bismuthane (PubChem 2015).

7.6.2 Toxicology Data

Bismuth compounds are generally poorly absorbed from the gastrointestinal tract or when applied to the skin, even if the skin is abraded or burned. Most ingested bismuth is excreted in the feces, with the remainder being excreted in the urine. The kidney is the principal target organ (HSDB 2002a).

Bismuth is believed to function via binding to sulfhydryl groups, especially in the CNS, resulting in loss of white matter, specifically Purkinje cells, and encephalopathy. Bismuth compounds also cause degeneration of the proximal tubules of the kidney, resulting in nephrotoxicity. Bismuth may have a protective effect on the gastric mucosa; it inhibits growth of *Helicobacter pylori,* associated with ulcers. Ingestion of bismuth products is common; toxicity from bismuth is rare and deaths have not been reported (HSDB 2002a).

7.6.2.1 Oral

No experimental data for acute or chronic oral toxicity for Bi_2O_3 were found.

Absorbed bismuth has a plasma half-life of about 5 days in humans (Hardman et al. 1996).

7.6.2.2 Inhalation

No experimental data were found. Bismuth particulates should find their way into the general circulation after inspiration in the lungs.

7.6.2.3 Dermal

No experimental data were found. Use of bismuth compounds as surgical pastes indicates a lack of dermal toxicity. Bismuth compounds are poorly absorbed by the skin, even when the skin is abraded or burned (HSDB 2002a).

7.6.2.4 Ocular

No experimental data were found.

7.6.2.5 Development and Reproduction

Passage of soluble bismuth into the amniotic fluid and fetus has been documented. Traces of soluble bismuth can be found in milk and saliva (Klaassen et al 1995).

There are two reported cases of pregnant women with acute bismuth poisoning who had normal pregnancies and children. Bismuth is known to cross the placenta, but in developmental experiments involving chickens, no birth defects were noted (HSDB 2002a).

Embryotropic effects of bismuth were studied in rats and mice. An increase in embryonic mortality and lag in development of fetuses were found. A significant increase in aberrations was noted at a concentration of 53.3 mg Bi/m^3 (HSDB 2002a).

7.6.2.6 Neurotoxicity

Bismuth exposure has been noted to result in CNS effects. Symptoms of cranial nerve damage include loss of balance, visual function, smell, taste, and facial sensations. Evaluation of CNS effects can be performed through neuropsychological assessment, which consists of a clinical interview and administration of standardized personality and neuropsychological tests. Areas of neuropsychological test batteries focus include memory and attention, visuoperceptual, visual scanning, visuospatial, and visual memory, motor speed and reaction time. Nerve damage may be assessed through physical examination, including smell assessment, vision assessment, facial and trigeminal nerve assessment, vestibular assessment, and hearing assessment (HSDB 2002a).

7.6.2.7 Genotoxicity

Mutagenic effects were studied by counting chromosomal aberrations of somatic, bone marrow cells in mice and rats. A significant increase in the rate of aberrations was noted at a concentration of 53.3 mg Bi/m^3 (HSDB 2002a).

7.6.2.8 Carcinogenicity

No experimental data were found. Bismuth salts are not anticipated to be carcinogenic.

7.6.2.9 Ecotoxicology

7.6.2.9.1 Fate and Transport

Bismuth is converted to insoluble forms under alkaline conditions. The conversion of soluble bismuth to insoluble salts limits its transport and bioconcentration in aquatic organisms. Bismuth has been detected in surface waters and sediment. Bismuth is not expected to volatilize from moist or dry soil (HSDB 2002a).

7.6.2.9.2 Ecotoxicity

No experimental data were found.

7.6.2.9.3 Degradation/Treatment

As an element, bismuth is not subject to degradation. In aerated water, bismuth oxidizes to yellow Bi_2O_3 by way of $Bi(OH)_3$. In the presence of atmospheric CO_2, white $Bi_2(CO_3)_3$ forms (HSDB 2002a).

7.7 Red Iron Oxide [Ferric oxide; Fe_2O_3]

7.7.1 General Information

Known more properly by the names ferric oxide or iron(II) oxide, Fe_2O_3 is the common form of iron oxide. It is red-brown in color. Fe_2O_3 can exist in several polymorphs; in the main forms, α and γ, iron adopts octahedral coordination chemistry. That is, each Fe atom is bound to 6 oxygen ligands (Cotton and Wilkinson 1972).

7.7.2 Toxicology Data

7.7.2.1 Oral
The oral LD_{50} in rats is reported to be >10,000 mg/kg (HSDB 2012a). No chronic exposure data were found.

7.7.2.2 Inhalation
Inhalation studies represent the preponderance of systematic studies conducted on iron oxide particulates, including nanoparticles. These studies have generally found no long-term systemic impact from inhalation of ferric oxide. However, chronic exposure should be avoided as the half-life for clearance of iron particles is 33 days in the rat, suggesting repeated exposure could cause build-up of particulates in the lungs with resulting loss of lung effectiveness (HSDB 2012a).

Bronchoalveolar lavage (BAL) was used to sample lung cells and biochemical components in the lung air spaces at various times from 1 to 91 days after intrapulmonary instillation of 2.6 µm diameter iron oxide particles in human subjects. The instillation of particles induced transient acute inflammation during the first day post-instillation (PI), characterized by increased numbers of neutrophils and alveolar macrophages as well as increased amount of protein, lactate dehydrogenase, and interleukin-8 in BAL fluids. The response was subclinical and was resolved within 4 days PI. The particles contained small amounts of soluble iron (240 ng/mg) and possess the capacity to catalyze oxidant generation *in vitro* (Lay et al. 1999).

Exposure to iron oxide dust and fumes can cause metal fume fever, which is a flu-like illness with symptoms of metallic taste, fever and chills, aches, chest tightness, and cough (HSDB 2012a).

7.7.2.3 Dermal
No data were found.

7.7.2.4 Ocular
Ocular irritation is expected to result from the particulate nature of ferric oxide.

7.7.2.5 Development and Reproduction
No data were found.

7.7.2.6 Genotoxicity
An Ames assay conducted on ferric oxide using *Salmonella typhimurium* strains TA100, TA94, and TA98 at concentrations from 2,000 to 50,000 µmol/plate, both with and without metabolic activation, failed to produce a genotoxic response (HSDB 2012a).

Garry et al. (2003) used the comet assay to measure DNA single-strand breaks in four cell types— alveolar macrophages, lung cells, peripheral lymphocytes, and hepatocytes—of OFA Sprague-Dawley rats 24 hours after endotracheal instillation of a single dose of ferric oxide (0.75 mg). No damage was observed in cells from the four investigated organs in rats.

7.7.2.7 Carcinogenicity
Evidence for carcinogenicity in humans is inadequate; ferric oxide is not classifiable as to its

carcinogenicity to humans. There is evidence suggesting lack of carcinogenicity in animals (HSDB 2012a).

Ferric oxide particles may function as co-carcinogens, as exposure to ferric oxide particles coated with benzo[a]pyrene (BaP) results in a decreased latency and an increased incidence in the production of lung tumors in hamsters compared to the administration of BaP alone (Greife and Warshawsky 1993).

7.7.2.8 Ecotoxicology

7.7.2.8.1 Fate and Transport

Due to general lack of solubility, ferric oxide is not expected to be mobile in the environment, and is, in fact, ubiquitous since iron is an extremely common element in the Earth's composition. Partition to the atmosphere is possible only in the particulate form. Ferric oxide will not bioaccumulate in aquatic species.

7.7.2.8.2 Ecotoxicity

The 2-day LD_{50} for exposure to *Ceriodaphnia dubia* is 200 mg/L. Toxicity data are also available for mayflies (*Cloeon dipterum*) where the LD_{50} is >40 mg/L. The 48-hour EC_{50} for sea urchins (*Paracentrotus lividus*) is 0.1 mg/kg body weight (ECOTOX 2017).

A no observed effect level (NOEL) for domestic chickens (*Gallus domesticus*) for a 21-day exposure is 480 mg/kg feed (ECOTOX 2017).

7.7.2.8.3 Degradation/Treatment

Ferric oxide is not subject to environmental degradation.

7.8 Black Iron Oxide [Fe_3O_4]

7.8.1 General Information

Fe_3O_4 is a mixed Fe(II)-Fe(III) oxide that occurs in nature in the form of black, octahedral crystals of the mineral magnetite. Fe_3O_4 is one of three naturally-occurring oxides of iron, the other two being FeO and Fe_2O_3. All three substances tend to be non-stoichiometric, but the formulas indicated are the preferred representations. Fe_3O_4 has electrical conductivity 10^6-times that of Fe_2O_3, probably due to rapid valence oscillation between the Fe sites (Cotton and Wilkinson 1972). Synonyms for this compound include triiron tetraoxide, magnetic black, iron black, and magnetite (Fe_3O_4), among others. The structure is sometimes represented with two additional hydrogen atoms. The dihydro form of the compound is marketed medically as ferumoxytol, which is an injectable form of iron used to treat iron deficiency anemia in people with chronic kidney disease (Drugs.com 2013, ChemID*plus* 2013).

7.8.2 Toxicology Data

Iron is an essential element required by all forms of life. The recommended daily iron intake in the U.S. ranges from 10 mg for infants up to 6 months of age to a maximum daily intake of 18 mg for males 11–18 years old and females 11–50 years old (HSDB 2005b).

7.8.2.1 Oral

Ingested iron is irritating to the gastrointestinal mucosa, with corrosive injury to the stomach potentially leading to pyloric stenosis (narrowing of the opening of the stomach to the small intestine) or gastric scarring. Early symptoms of acute iron overload are vomiting, diarrhea, abdominal pain and gastrointestinal hemorrhage. In fatal cases, hemorrhagic gastroenteritis and hepatic damage are prominent autopsy findings (HSDB 2005b).

Respiratory failure is the immediate cause of death from iron overdose in laboratory animals. Clinical signs preceeding death are anorexia, oligodipsia (absence of thirst), oligouria (absence of urine production), alkalosis, diarrhea, loss of body weight, hypothermia, and alternating irritability and depression (HSDB 2005b).

As little as 1–2 g of iron may cause death in a child; the estimated fatal dose for an adult for soluble ferric (Fe(III)) salts is 30 g/kg (HSDB 2005b).

7.8.2.2 Inhalation

Inhalation of iron salts is irritating to the respiratory tract (HSDB 2005b).

Pulmonary siderosis (pneumoconiosis from inhalation of iron dust) results from inhalation of iron dust or fumes, but it falls into the group of pneumoconiosis in which the pulmonary reaction is minimal, despite heavy dust load (HSDB 2005b).

7.8.2.3 Dermal

Iron salts are regarded as skin irritants (HSDB 2005b).

7.8.2.4 Ocular

No data were found. Particulate iron oxide can reasonably be expected to be an eye irritant.

7.8.2.5 Development and Reproduction

The maternal placenta appears to protect the developing fetus from iron overload. Case reports of pregnant women who have received early aggressive treatment for iron overdose (as a result of treatment for iron deficiency anemia) have described good fetal outcomes (HSDB 2005b).

7.8.2.6 Genotoxicity

Incubation of iron with isolated rat liver nuclei stimulated fragmentation of single-stranded DNA; iron(II) chloride was about twice as active as iron(III) chloride (HSDB 2005b).

7.8.2.7 Carcinogenicity

No data were found.

7.8.2.8 Ecotoxicology

7.8.2.8.1 Fate and Transport

Iron salts are ubiquitous in the environment and are a major constituent of soils. Iron is the fourth most abundant metal in the earth's crust. Iron would exist in the particulate phase in the atmosphere and is readily removed by either wet or dry deposition. In general, metal cations in solution are attracted to the negatively-charged surfaces of soil particles. Iron(III) ions have

been shown to be strongly retained by the humic and fulvic acid fractions of soils (HSDB 2005b).

Bioconcentration factors for iron were reported to be 0.8, 0.6, 0.002, and 0.003 for chironomids, macrophytes, perch, and crucian carp, respectively (HSDB 2005b).

7.8.2.8.2 Ecotoxicity

LC_{50} and EC_{50} values have been reported for various species as follows (HSDB 2005b):

- 24-hour EC_{50} in diatoms (*Thalassiosira pseudonana*), 73.07 mg/L;
- 24-hour LC_{50} in mayflies (*Leptophlebia marginata*), 73.07 mg/L;
- 5-day EC_{50} in mayflies (*Leptophlebia marginata*), 8.48 mg/L;
- 4-day EC_{50} in duckweed (*Lemna minor*), 3.7 mg/L;
- 48-hour EC_{50} in a haptophyte (*Isochrysis galbana*), 8.5 mg/L;
- Less than 96-hour LC_{50} in catfish (*Ictalurus punctatus*), >500 mg/L;
- 48-hour EC_{50} in the dinoflagellate *Gymnodinium splendens*, 17.5 mg/L; and
- 96-hour LC_{50} in carp (*Cyprinus carpio*) of 0.56 mg/L.

7.8.2.8.3 Degradation/Treatment

Iron is elemental and therefore not subject to degradation; however, changes in valence are possible. Most iron found in the environment is oxidized to Fe(III) (HSDB 2005b).

7.9 Tungsten [W], tungsten trioxide [WO_3] and manganese tungstate [$MnWO_4$]

7.9.1 General Information

Tungsten is a steel-gray, hard, brittle metallic solid. Its chemical symbol, “W,” is derived from *Wolfram,* the original German name for the material. Oxidation of elemental W results in the formation of WO_3, a lemon-yellow solid with a melting point of 1,200ºC. WO_3 will dissolve in basic solutions to form tungstate, WO_4^{2-} (Cotton and Wilkinson 1972). Tungsten trioxide or tungstic oxide is a yellow to yellow-orange crystalline solid that becomes dark orange when heated but returns to its original color on cooling. Principal uses are in the manufacture of tungstates used for x-ray screens and in fireproofing fabrics, and as a yellow pigment in ceramics. Synonyms include tungsten oxide, tungsten(VI) oxide, tungstic acid anyhydride, tungstic anyhydride, and tungstic oxide (HSDB 2005c).

Manganese tungstate is a solid yellow powder (ESPI 2008). Synonyms include manganese tungsten oxide, manganese(II) tungsten oxide and manganese tungstate (ChemID*plus* 2017b).

7.9.2 Toxicology Data

The different oxides of tungsten vary considerably in their toxic effects: elemental tungsten has

very little toxicity, but the tungstate anion (WO_4^{2-}) is considerably more toxic. It is believed that tungsten may substitute for molybdenum in some enzymatic systems, e.g., xanthine dehydrogenase and xanthine oxidase (ATSDR 2005a), resulting in impaired enzymatic function.

Inhalation, oral, and parenteral injection studies in laboratory animals all indicate that absorbed tungsten is rapidly eliminated from the blood and quickly excreted in large quantities in the urine. Studies using radiolabeled tungsten indicate about 90% excretion in the urine over a 14-hour period (ATSDR 2005a).

Few data exist for $MnWO_4$; toxicological effects are presumed to be a combination of effects attributable to manganese and tungstate.

7.9.2.1 Oral

Manganese compounds are poorly absorbed from the gastrointestinal tract (ESPI 2008). Tungsten metal is considered to be moderately toxic. The probable lethal oral human dose is between 0.5 and 5 g/kg (HSDB 2005c).

The intraperitoneal LD_{50} in rats for elemental tungsten is reported to be 5,000 mg/kg body weight (ATSDR 2015).

Feeding studies with both rats and rabbits where the test substance is delivered in the food indicate that WO_3 present at a level of 0.5% is not lethal to either species but will result in a decreased growth rate. A higher concentration of 3.96% is lethal to both species (HSDB 2005c).

Tungstate is the most toxic form of tungsten, with an oral LD_{50} of 223–255 mg/kg (ATSDR 2015). $MnWO_4$ is classified as Category 3 for acute toxicity under the GHS (Fisher Scientific 2015a).

7.2.9.2 Inhalation

Elemental tungsten is reported to be a respiratory irritant (HSDB 2005c). Excessive exposure may lead to pulmonary fibrosis, although this is primarily found in “hard metal” work involving tungsten or tungsten carbide alloy and is not anticipated to be a significant concern here (O’Neil 2006, ATSDR 2005a).

Intratracheal instillation of tungsten metal and tungsten carbide dust in guinea pigs at 50 mg/week for 3 weeks found the dust to be relatively inert (ATSDR 2015).

Occupational settings are the primary source of inhalation exposure to tungsten compounds, especially those involved in the machining of “hard metal,” a tungsten or tungsten carbide alloy. Based on the presence of tungsten oxide fibers in air samples taken in some hard metal facilities and demonstrations that tungsten oxide fibers are capable of generating hydroxyl radicals in humanlung cells *in vitro*, it has been suggested that tungsten oxide fibers may contribute to the development of pulmonary fibrosis in hard metal workers, although respiratory and neurological effects are traditionally attributed to cobalt (ATSDR 2005a).

Inhalation is the primary route of potential exposure for $MnWO_4$. Inhalation of $MnWO_4$ may cause irritiation of the respiratory tract and mucous membranes. Extended duration of exposure

may result in manganism (ESPI 2008). (See paragraph 7.3 for a more complete discussion of manganism.)

7.2.9.3 Dermal

Elemental tungsten is reported to be a dermal irritant (HSDB 2005c). Dermal exposure may result in localized irritation (ATSDR 2005a).

Death resulted in rabbits exposed to a 5% tungsten chloride solution in single doses of 100–1,000 mg/kg, indicating dermal absorption of tungsten compounds occurs to some extent (ATSDR 2005a).

$MnWO_4$ may cause dermal irritation (ESPI 2008) but is not known to be a dermal sensitizer (Fisher Scientific 2015a).

7.2.9.4 Ocular

Elemental tungsten and tungsten trioxide are reported to be ocular irritants (HSDB 2005c, ATSDR 2005).

$MnWO_4$ may cause ocular irritation (ESPI 2008). $MnWO_4$ is classified as Category 2A for ocular irritation under the GHS (Fisher Scientific 2015a).

7.2.9.5 Development and Reproduction

Powdered tungsten fed to weanling rats at levels of 2, 5, and 10% of the diet resulted in no effect on growth rate of male rats but caused a 15% reduction in weight gain in females when compared to controls (HSDB 2005c).

Limited reports associate tungsten exposure with reproductive and developmental effects such as decreased sperm motility, increased embryotoxicity, and delayed skeletal ossification in animals (ATSDR 2005a). There are no known developmental or reproductive effects for $MnWO_4$.

7.2.9.6 Neurotoxicity

Information in humans is restricted to a single account of nausea, followed by seizure and 24-hour coma in a male subject who had accidentally consumed a mixture of beer and wine that had been poured into the hot barrel of a 155-mm gun as part of an initiation ceremony. Inductively-coupled plasma emission spectrometry indicated very high concentrations of tungsten in the drink, as well as in the male's gastric content, blood, and urine. Blood levels remained high (>0.005 mg/L) until day 13, despite hemodialyses, and in urine until day 33. The subject recovered fully (Marquet et al. 1997).

7.2.9.7 Genotoxicity

No data were found for elemental tungsten, tungsten trioxide, or manganese tungstate. Guilbert et al. (2011) reported increased DNA damage within the bone marrow of C57BL/6J mice that received tap drinking water to which an unspecified form of tungsten had been added at 15–200 mg/L for 8 weeks. However, other studies have failed to reveal any significant genotoxicity of tungsten compounds (ATSDR 2015).

7.2.9.8 Carcinogenicity

A cancer cluster observed in Churchill County, Nevada, was suspected to be linked to tungsten in the drinking water; however, no statistically significant association was found between the exposure to tungsten in the drinking water and the occurrence of leukemia (ATSDR 2005a).

Tungsten, tungsten trioxide, and manganese tungstate are not classifiable as carcinogens by the IARC, the EPA, or the ACGIH (ATSDR 2005a).

7.9.2.9 Ecotoxicology

7.9.2.9.1 Fate and Transport

Tungsten exists in several oxidation states, the most stable of which is +6, with lower oxidation states being somewhat unstable. There are no reports of tungsten organic complexes, but tungsten has a strong tendency to form complexes exemplified by a large series of heteropoly acids formed with oxides of phosphorous, arsenic, vanadium, and silicon, among others. Tungsten may also exist in more than one oxidation state in some compounds (HSDB 2005c).

If released to soil or water, tungsten compounds will generally exhibit low mobility due to binding of ions to suspended solids in sediments. Tungsten compounds are expected to exist as ions or insoluble solids in the environment, and volatilization from wet or dry surfaces is not expected.

Ingested tungsten compounds are excreted relatively rapidly, and bioaccumulation is not expected, as most compounds are insoluble.

High concentrations of tungsten or its compounds may result in detectable mobility in the environment. Concentrations of tungsten in soil as high as 2,080 mg/kg soil were detected in soil from the Massachusetts Military Reservation small arms ranges after the use of lead bullets was banned by the EPA, and tungsten-nylon bullets were used in their stead. Tungsten concentrations decreased rapidly with depth, at least by a factor of 10 at 25 cm, but were still detectable to a depth of 150 cm. Areas outside of the small arms ranges had tungsten concentrations of 1.3–1.5 mg/kg (Clausen and Korte 2009).

In water, tungsten is progressively oxidized to the W(VI) oxidation state according to the scheme below (equations adapted from ATSDR 2005a):

$W + 2OH^- \rightarrow WO^+ + H_2O + 3e^-$

$WO^+ + 2OH^- \rightarrow WO_2 + H_2O + e^-$

$WO_2 + OH^- \rightarrow WO_3H + e^-$

$WO_3H + OH^- \rightarrow WO_3 + H_2O + e^-$

$WO_3 + OH^- \rightarrow HWO_4^{-2}$

$HWO_4^{-2} \rightarrow WO_4 + H_2O$

Accompanying reduction of oxygen: $O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$

Under alkaline conditions, elemental tungsten can be oxidized to WO_3 and ultimately WO_4^{2-}. This change is accompanied by a decrease in the pH of the involved medium, either water or

soil. Tungsten binds with soils in proportion to the organic content of the soil; adsorption is greater with greater organic content. Binding of tungsten to some soils (e.g., montmorillonite and illite) occurs through cooperative adsorption, probably through polymerization of tungstates to form isopolytungstates. These binding processes have the effect of limiting the mobility of tungsten in soils (ATSDR 2005a). Leachability and mobility tests conducted on bullets made of tungsten or tungsten-tin that had been crushed to simulate degradation indicated little leaching from topsoil (i.e., high organic content) but increased leaching from sandy soils (Department of the Army (DA) 2000).

Plants are known to take up and accumulate tungsten in substantial amounts. The extent of accumulation appears to be directly related to the tungsten content of the soil, regardless of the tungsten source, and varies widely with the plant genotype. Certain plants, e.g., tomatoes, act as excluders of tungsten, particularly in the presence of molybdenum. Other plants appear to at least accumulate tungsten in accordance with the local soil or atmospheric concentrations (Koutsospyros et al. 2006).

If released to soil, tungsten compounds will have moderate to low mobility based upon sorption coefficients ranging from 10 to 50,000 at pHs from 5 to 6.5. Tungsten compounds will exist as ions or insoluble solids in the environment, so volatilization from soil or water is not an important fate process. Due to their ionic character and low vapor pressures, tungsten compounds will not volatize from dry soil (ATSDR 2005a).

If released to air, most tungsten compounds have low vapor pressures and will exist solely in the particulate phase in the atmosphere. Particulate-phase tungsten compounds may be removed from the atmosphere by wet or dry deposition (ATSDR 2005a).

Due to its chemical nature, tungsten is not expected to bioaccumulate in animal tissues, but data are lacking.

Due to its insolubility, $MnWO_4$ is not expected to be mobile in the environment, will not partition to the atmosphere from water or soil, and will not bioaccumulate. Any $MnWO_4$ present in the atmosphere is expected to be in particulate form.

7.9.2.9.2 Ecotoxicity

Due to insolubility and lack of bioavailability, elemental tungsten is not toxic. Several data points for tungsten converted to tungstate have been reported in ECOTOX but will not be reported here because the anticipated amount of tungstate resulting from *in situ* oxidation is anticipated to be very small.

The concentration of tungsten in plants is low. Beans were found to incorporate tungsten when grown in soil amended with 1, 5, or 10% by weight tungsten metal or tungsten trioxide powder. The uptake was higher for tungsten metal than its oxide (1,100 mg/kg for metal versus 820 mg/kg for oxide at 10-weight percent) and increased with soil concentration in an apparently symptotic manner (Bowen 1960). Rye grass was also found to take up tungsten from soil into the plant stem (DA 2000).

Plant toxicity from tungsten has also been reported in the literature. Accumulation and toxicity of

tungsten on rye grass has been reported to result in plant death approximately 4 weeks after germination. Sequestration of excess tungsten in peripheral cell layers appears to be a common mechanism of plant metal accumulation, possibly resulting in less harm to the plant, or as a defense against pathogens or herbivores (Koutsospyros et al. 2006). Due to insolubility, $MnWO_4$ is not expected to be toxic to free-swimming aquatic species. Effects on aquatic and terrestrial plants are unknown; manganese is toxic to plants in higher concentrations.

7.9.2.9.3 Degradation and Treatment

As an element, tungsten is not subject to degradation *per se* but can engage in reactions in the environment that alter its chemical form and properties. Under alkaline conditions, elemental tungsten can be oxidized to WO_3 and ultimately to WO_4^{2-}. $MnWO_4$ is not subject to degradation in the environment but could engage in ion exchange reactions. WO_4^{2-} is the most stable of the tungsten oxides.

7.10 Titanium [Ti]

7.10.1 General Information

Titanium is a dark gray, lustrous metal that exists in a hexagonal crystalline form below temperatures of 882.5 ºC, and in a cubic form above that temperature. It is brittle when cold but malleable when hot. Titanium is ductile only when free of oxygen and will combine with nitrogen at 800 ºC (HSDB 2003a).

7.10.2 Toxicology Data

Most ingested titanium is eliminated without absorption. In humans, titanium is probably excreted in the urine at a rate of about 10 µg/L. However, high urinary losses of 0.41 and 0.46 mg/day (30-day mean), respectively, were reported in two adults. Titanium is essentially non-toxic, a fact demonstrated by its use in surgical applicances and medical prosthetics (HSDB 2003a).

7.10.2.1 Oral

No oral toxicity data were found.

7.10.2.2 Inhalation

Inhalation of titanium dust has caused only slight lesions of the lung. Intratracheal injections of 50 mg of metallic titanium failed to demonstrate development of fibrosis up to 11 months post-injection (HSDB 2003a).

7.10.2.3 Dermal

No data were found.

7.10.2.4 Ocular

No data were found.

7.10.2.5 Development and Reproduction

Titanium has been found in the infant kidney and lung, indicating transplacental transfer; however, there are no indications of developmental or reproductive toxicity (HSDB 2003a).

7.10.2.6 Genotoxicity
No data were found. Titanium metal is not expected to be mutagenic.

7.10.2.7 Carcinogenesis
Titanium is not considered to be carcinogenic; its only carcinogenic effect has been the development of fibrosarcomas at the injection site of exposed rats (HSDB 2003a).

7.10.2.8 Ecotoxicology

7.10.2.8.1 Ecotoxicity
Titanium is non-reactive with water but is soluble in dilute acids. This lack of solubility is expected to limit the transport of titanium in groundwater systems. Titanium is not volatile and will not partition into the atmosphere from either wet or dry soil. Titanium is not expected to bioconcentrate, and in the atmosphere, it is expected to exist exclusively as a particulate.

7.10.2.8.2 Ecotoxicity
No data were found. Due to its lack of solubility, titanium is not expected to exhibit ecotoxicity.

7.10.2.8.3 Degradation and Treatment
Titanium is chemically almost completely inert and is, therefore, not subject to degradation or reaction to other chemical species.

7.11 Titanium hydride [TiH_2]

7.11.1 General Information
The primary synonym for titanium hydride is titanium dihydride. TiH_2 is an intermediate in a new process for isolating titanium metal from titanium minerals (slags) with significantly reduced energy consumption. The method involves direct reduction of the minerals, using magnesium hydride to form titanium hydride, with titanium metal being purified by a series of chemical leaching steps (Fang et al. 2013). TiH_2 powders are used in the manufacture of orthopedic NiTi scaffolds for prosthetics (Wu et al. 2011). TiH_2 is also used in various other manufacturing processes, including dental implants. TiH_2 will react with water or upon heating to release hydrogen gas, presenting a flammability and explosion risk.

7.11.2 Toxicology Data
Very few toxicology data are available for TiH_2. However, there are other hydrides that may provide clues to possible TiH_2 effects. Metal hydrides are chemical reducing agents.

Dopp et al. (2004) discussed toxicity of various metals, including titanium, and their tendency to form organo-halides via metabolism by gastic microorganisms. Since TiH_2 is anticipated to be more reactive and subject to derivatization due to the hydride substitution, it may have a greater tendency to form these toxic metabolites. However, this should not be an issue for human health and environmental toxicity in the absence of chronic exposure. Biomethylation is a common process in the biogeochemistry of the earth's surface and has been described in natural systems for several potentially toxic metals.

7.11.2.1 Oral
Ingestion of TiH_2 is considered non-toxic (ESPI 2005).

7.11.2.2 Inhalation
Inhalation of dust may cause irritation to the upper respiratory system (ESPI 2005).

7.11.2.3 Dermal
Prolonged or repeated exposure may cause irritation (ESPI 2005).

7.11.2.4 Ocular
Prolonged or repeated exposure may cause irritation (ESPI 2005).

7.11.2.5 Development and Reproduction
No data were found.

7.11.2.6 Genotoxicity
No data were found.

7.11.2.7 Carcinogenicity
No data were found.

7.11.2.8 Ecotoxicology

7.11.2.8.1 Fate and Transport
No data were found.

7.11.2.8.2 Ecotoxicity
No data were found.

7.11.2.8.3 Degradation and Treatment
No data were found.

7.12 Potassium nitrate [KNO_3]

7.12.1 General Information
For most nitrate salts, it is the nitrate anion and not the cation (e.g., sodium, potassium, calcium) that is considered to be the toxicant. Sodium and potassium nitrate are often considered together or viewed as interchangable in toxicity assessments, although there may be exceptions when large quantities are involved, and large quantities of potassium can cause neurological effects.

7.12.2 Toxicology Data

7.12.2.1 Oral
In humans, death and other severe effects of nitrate ingestion are generally associated with doses in excess of 10 g nitrate, corresponding to 33–150 mg nitrate/kg. Clinical signs of acute toxicity include violent gastroenteritis, anemia, methemoglobinemia, nephritis, vomiting, vertigo,

muscular weakness, irregular pulse, convulsions and collapse. Methemoglobinemia is the most common symptom of potassium nitrate exposure in humans. Sensitive human subpopulations include infants, especially those younger than 3 months of age, and individuals with a deficiency of the enzyme glucose-6-phosphate dehydrogenase or with hereditary deficiencies in methemoglobin reductase (HSDB 2007).

The LD_{50} values for rats and rabbits have been determined to be 3,750 mg/kg and 1,901 mg/kg respectively, and the estimated minimum lethal dose for cattle and sheep is 1,000 mg/kg (Sax and Lewis 1989).

No systematic toxicology studies were found at the subacute level; however, there are considerable data on the toxicity of feed containing high nitrate levels (>1 percent by weight) to livestock (sheep, cows, horses, etc.) (HSDB 2007).

In a study by Til et al (1988), 6-week-old Wistar rats were given 100, 300, 1000, and 3000 mg potassium nitrite/L in drinking water for 90 days. Methemoglobin was significantly increased and plasma alkaline phosphatase activity was decreased in both sexes, plasma urea was increased in males at the 300 mg/kg treatment level.

7.12.2.2 Inhalation
Potassium nitrate is irritating to the respiratory tract (HSDB 2007).

7.12.2.3 Dermal
Potassium nitrate is irritating to the skin (HSDB 2007).

7.12.2.4 Ocular
Potassium nitrate is irritating to the eyes (HSDB 2007).

7.12.2.5 Development and Reproduction
Female CD-1 mice were administered potassium nitrate for 10 days. At the highest dose of 400 mg/kg, no significant differences in survival, number of pregnancies, number of abortions, resorptions, dead fetuses, or average fetal weight were observed (HSDB 2007).

Female guinea pigs were given 0, 300, 2500, 10,000, or 30,000 parts per million (ppm) potassium nitrate in drinking water for 204 days (Sleight and Atallah 1968). Decreases in the number of litters and the number of live births were observed in animals in the 30,000-ppm dose group, which were estimated to have received a dose equivalent to 1,130 mg/kg nitrate. One female in this dose group died with four mummified fetuses *in utero*. The fetal deaths were attributed to hypoxia caused by maternal methemoglobinemia.

7.12.2.6 Genotoxicity
Potassium nitrate was negative in the Ames assay under aerobic conditions either with or without metabolic activation. It was also found to be negative in a Chinese hamster fibroblast assay (HSDB 2007).

7.12.2.7 Carcinogenicity
Nitrates can be transformed to nitrites by certain microorganisms in the soil and by

microorganisms found in the mouth and stomach, followed by nitrosation of secondary amines and amides in the diet. The resulting nitrosamines are mutagenic, but humans are naturally exposed to the precursors as a part of a normal diet. The average Western diet contains 1–2 mmol nitrate/person/day (Hotchkiss 1992).

According to the U.S. Environmental Protection Agency (EPA), available information on the carcinogenic potential of nitrates is equivocal. The results of some carcinogenicity studies suggest that nitrates may cause tumors in laboratory animals while others do not (EPA 1991). The possible carcinogenicity of nitrate depends on the conversion of nitrate to nitrite and the reaction of nitrite with secondary amines, amides, and carbamates to form N-nitroso compounds that are carcinogenic (Bouchard et al. 1992).

7.12.2.8 Ecotoxicology

7.12.2.8.1 Fate and Transport

Potassium nitrate is readily soluble in water and will be solubilized when water is present. The anion is an essential nutrient for plants and, therefore, will be readily removed from soil when plants are present. Small discharges to surface water are also expected to be taken up by plants, but larger discharges can result in toxicity to aquatic species or to ecological upset due to rapid plant (algae) growth and subsequent death. Nitrates can also be metabolized by bacteria, especially in anaerobic environments (HSDB 2007).

7.12.2.8.2 Ecotoxicity

The LC_{50} for a 28-day exposure to annelid worms averages 2,230 µg/L (Reish 1970). The 24-, 48-, and 96-hour LC_{50} for adult female mosquitofish (*Gambusia affinis*) has been determined as 58,500; 31,100; and 22,500 µg/L; respectively (Wallen et al. 1957).

Reproduction rates of *Hydra attenuata* were evaluated at exposure levels of 50, 150, and 250 mg nitrate/L. Growth rates were comparable to controls for the two lower dose rates; however, growth rates were retarded at 250 mg/L. Clubbing of tentacles was not observed at the high dose. Concurrent tests were run with sodium and ammonium nitrates; the potassium salt was found to be the least toxic of the three nitrates. The cation had a considerable effect on the toxicity of the solution (HSDB 2007).

The 96-hour LC_{50} for *Daphnia magna* is 39 mg/L. The LC_{50} for a 24-hour exposure in Bluegill (*Lepomis macrochirus*) is 5,500 mg/L (HSDB 2007).

At concentrations of potassium nitrate up to 1,035 mg KNO_3/L, development of loach (*Misgurnus fossilis*) embryos through resorption of the yolk sac was similar to controls. At 2068–2586 mg KNO_3/L, prolarvae hatched but then died. Concentrations of 5,171 mg/L stopped all development (HSDB 2007).

7.12.2.8.3 Degradation and Treatment

Potassium nitrate is readily taken up by both terrestrial and aquatic plants as an essential nutrient. It will also be consumed by bacteria (HSDB 2007).

7.13 Zirconium [Zr]

7.13.1 General Information
Zirconium is a metallic solid grayish-white in color; the amorphous powder is blue-black (O'Neil 2006). Zr will react exothermically with many other elements and may spontaneously combust or explode (HSDB 2006a).

7.13.2 Toxicology Data
Zr has a low order of toxicity; there are no characteristic signs of Zr poisoning (HSDB 2006a).

7.13.2.1 Oral
No data were found.

7.13.2.2 Inhalation
Pulmonary granuloma has been reported in zirconium workers; however, a study of 22 workers exposed to fumes from a Zr reduction process for 1 to 5 years revealed no abnormalities related to Zr (HSDB 2006a).

7.13.2.3 Dermal
No data were found.

7.13.2.4 Ocular
Zr may cause mechanical irritation to the eyes (HSDB 2006a).

7.13.2.5 Development and Reproduction
No data were found.

7.13.2.6 Genotoxicity
No data were found.

7.13.2.7 Carcinogenicity
Zr is not classifiable as a human carcinogen (HSDB 2006a).

7.13.2.8 Ecotoxicology

7.13.2.8.1 Fate and Transport
Zirconium exists in nature in combined form only. Zr occurs in the minerals zircon, malacon, baddeleyite, zirkelite, and eudialyte. It is also found in rare-earth minerals and in monazite sand. Due to its mineral form, Zr does not pose an environmental fate or transport hazard (HSDB 2006a).

7.13.2.8.2 Ecotoxicity
No data were found.

7.13.2.8.3 Degradation and Treatment
No data were found.

7.14 Polytetrafluoroethylene [PTFE]

7.14.1 General Information

Polytetrafluoroethylene (Teflon™) (shown in Figure 1) is produced by polymerization of the monomer tetrafluoroethylene. Polytetrafluoroethylene is a common product, finding use in many household and commercial applications requiring low friction coefficients. Polytetrafluoroethylene polymers typically contain more than 20,000 monomer units (O'Neil 2006).

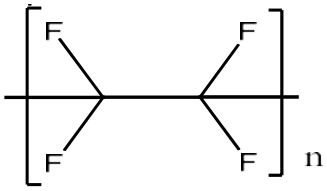

Figure 1. PTFE

7.14.2 Toxicology Data

Finished polytetrafluoroethylene is inert under ordinary conditions. There have been reports of polymer fume fever and pulmonary edema in humans exposed to either unfinished product or pyrolysis products. Symptoms of polymer fume fever resemble influenza, and may include chills, headaches, rigor-like shaking of limbs, mild respiratory discomfort, and high fever. Symptoms typically disappear within 48 hours if the person is removed from the exposure source and allowed to rest (HSDB 2002b).

Ingredients of polytetrafluoroethylene and pyrolysis products can produce toxic effects. Pyrolysis products include hydrofluoric acid (HF) and fluorophosgene (CF_2O). Smoking greatly increases the risk of exposure in workers (HSDB 2002b).

7.14.2.1 Oral

No LD_{50} has been determined, but no toxicity was noted in male and female rats fed polytetrafluoroethylene at concentrations of up to 25% in the diet for a 90-day period (HSDB 2002b).

7.14.2.2 Inhalation

Polytetrafluoroethylene is a solid and is inhalable only as a particulate. Combustion produces toxic gases reported to include octafluoroisobutylene, tetrafluoroethylene, hexafluoroethylene, hexafluoropropylene, and octafluorocyclobutane. Rats exposed to these products have shown signs of pulmonary irritation and edema, as well as diffuse degeneration of the brain, liver and kidneys (HSDB 2002b).

The LC_{50} for pyrolysis products in mice was determined to be less than 2g for a 30-minute exposure (HSDB 2002b).

The maximum allowable concentration of the monomer tetrafluoroethylene in rabbits was 6–8 mg/m^3 for a 3-month exposure (HSDB 2002b).

7.14.2.3 Dermal
No experimental data for polytetrafluoroethylene were found. The monomer tetrafluoroethylene is a dermal irritant (HSDB 2012b).

7.14.2.4 Ocular
No experimental data for polytetrafluoroethylene were found. The monomer tetrafluoroethylene is an ocular irritant (HSDB 2012b).

7.14.2.5 Development and Reproduction
No experimental data for Polytetrafluoroethylene were found. Polytetrafluoroethylene is not anticipated to be a developmental or reproductive toxicant.

7.14.2.6 Genotoxicity
No experimental data for polytetrafluoroethylene were found. The monomer tetrafluoroethylene is negative in the Ames test and several other tests for mutagenicity (HSDB 2012b).

7.14.2.7 Carcinogenicity
Polytetrafluoroethylene is not classifiable as to human carcinogenicity. There are no data for humans, and evidence in animals is inadequate (HSDB 2002b). The monomer tetrafluoroethylene is a confirmed animal carcinogen and is likely a human carcinogen (HSDB 2012b).

7.14.2.8 Ecotoxicology

7.14.2.8.1 Fate and Transport
Due to its chemical inertness and polymeric nature, polytetrafluoroethylene is not anticipated to be mobile in the environment.

7.14.2.8.2 Ecotoxicity
No experimental data were found. Polytetrafluoroethylene is not expected to pose an ecotoxicity hazard due to its chemical inertness.

7.14.2.8.3 Degradation and Treatment
Polytetrafluoroethylene is chemically inert, but at temperatures above 400°C, it will depolymerize with release of the monomer tetrafluoroethylene (O'Neil 2006).

7.15 Titanium dioxide [TiO_2]

7.15.1 General Information
TiO_2 is a white solid, found in nature in various minerals including rutile, anatase, octahedrite, brookite, ilmenite, and perovskite. TiO_2 possesses perhaps the greatest hiding power of all inorganic white pigments, leading to widespread use in this application. Applications include as a coating for welding rods, a paint pigment, inks and plastics, paper filling and coating, tanners' leather finishes, ceramics, and as a topical sunscreen.

7.15.2 Toxicology Data

7.15.2.1 Oral
Most ingested titanium is eliminated unabsorbed. In humans, titanium is probably excreted with the urine at a rate of about 10 µg/L (HSDB 2002c).

7.15.2.2 Inhalation
TiO_2 caused adenomas and a squamous cell carcinoma in the lungs when administered via inhalation to rats for a period of 24 months, 6 hours/day, 5 days/week. Exposure concentrations ranged up to 250 mg/m^3 (CCRIS 2010).

7.15.2.3 Dermal
No data were found. Dermal effects are not expected.

7.15.2.4 Ocular
No data were found. TiO_2 particulates would be expected to be irritating to the eye.

7.15.2.5 Development and Reproduction
There are no indications of developmental or reproductive toxicity.

7.15.2.6 Neurolotoxicity
No data were found. TiO_2 is not expected to be neurologically active.

7.15.2.7 Genotoxicity
TiO_2 was negative in the Ames mutagenicity test in *S. typhimurium* strains TA100, TA97, TA1535, TA1537, TA98, TA102 and *E. coli* strain WP2 UVRA with or without microsomal activation. A negative result was also achieved with the *in vitro* micronucleus test in Chinese Hamster Ovary (CHO) cells with or without microsomal activation. However, positive results were obtained by nano-TiO_2 in a human B-cell lymphoblastoid system and in transgenic mouse embryo fibroblasts (CCRIS 2010).

7.15.2.8 Carcinogenicity
TiO_2 caused adenomas and a squamous cell carcinoma in the lungs when administered to rats via inhalation for a period of 24 months, 6 hours/day, 5 days/week. Exposure concentrations ranged up to 250 mg/m^3. Oral administration did not result in cancers (CCRIS 2010).

7.15.2.9 Ecotoxicology

7.15.2.9.1 Fate and Transport
If released to soil or water, TiO_2 is not expected to be mobile due to its insolubility. Insoluble titanium compounds will not partition to the atmosphere from water or wet or dry surfaces. Any TiO_2 existing in the atmosphere will be in particulate form. Bioconcentration is not expected to occur in aquatic organisms due to the insolubility of the material (HSDB 2002c).

7.15.2.9.2 Ecotoxicity
No data were found. Ecotoxicity is not expected due to lack of solubility.

7.15.2.9.3 Degradation/Treatment
TiO_2 will not degrade in the environment due to its inorganic, elemental nature. Ti(IV) compounds will eventually oxidize into minerals, effectively removing them from environmental interactions (HSDB 2002c).

7.16 Titanium diboride [TiB_2]

7.16.1 General Information
TiB_2 is a gray ceramic powder with high hemolytic activity. It is also known as titanium boride (ChemID*plus* 2017).

7.16.2 Toxicology Data
Very few toxicology data are available for TiB_2.

7.16.2.1 Oral
According to a supplier's safety data sheet (SDS), TiB_2 is classified in category 4 for oral toxicity under the GHS (Federal Register 2012). No toxicity data were provided (Sigma-Aldrich 2014).

7.16.2.2 Inhalation
According to a supplier's SDS, TiB_2 is classified in category 4 for inhalation toxicity under the GHS (Federal Register 2012). No toxicity data were provided (Sigma-Aldrich 2014).

7.16.2.3 Dermal
According to a supplier's SDS, TiB_2 is classified in category 4 for acute dermal toxicity under the GHS (Federal Register 2012). No toxicity data were provided (Sigma-Aldrich 2014).

7.16.2.4 Ocular
No data were found.

7.16.2.5 Development and Reproduction
No data were found.

7.16.2.6 Genotoxicity
No data were found.

7.16.2.7 Carcinogenicity
According to a supplier's SDS, TiB_2 is not identified as a possible, probable, or confirmed carcinogen by the IARC, ACGIH, NTP, or OSHA (Sigma-Aldrich 2014).

7.16.2.8 Ecotoxicology

7.16.2.8.1 Fate and Transport
No data were found. Environmental mobility will presumably be limited by the insolubility of the compound.

7.16.2.8.2 Ecotoxicity
No data were found. Insolubility suggests there will be no toxic effects to wildlife.

7.16.2.8.3 Degradation/Treatment
Being an inorganic elemental compound, TiB_2 is not subject to environmental degradation but may be converted to other titanium salts.

7.17 Titanium carbide [TiC]

7.17.1 General Information
TiC is a grey solid “hard metal” most often used in manufacture of structural items (ESPI 2015).

7.17.2 Toxicology Data
Titanium compounds are generally considered to be poorly absorbed upon ingestion or inhalation. Dusts may be placed in the nuisance category (ESPI 2015).

7.17.2.1 Oral
No data were found.

7.17.2.2 Inhalation
Inhalation of TiC occurs primarily incidental to the manufacture of the material itself (HSDB 2002c). TiC dust may cause irritation if inhaled (ESPI 2015).

7.17.2.3 Dermal
No data were found.

7.17.2.4 Ocular
No data were found.

7.17.2.5 Development and Reproduction
No data were found.

7.17.2.6 Genotoxicity
No data were found.

7.17.2.7 Carcinogenicity
TiC is not identified as carcinogenic by either the NTP or IARC (ESPI 2015).

7.17.2.8 Ecotoxicology

7.17.2.8.1 Fate and Transport
TiC is not expected to be mobile in the environment due to its solid physical state. Any TiC present in the atmosphere will be present in the form of a dust or particles. Titanium is an insoluble, inert material and not expected to be bioconcentrated in the environment.

7.17.2.8.2 Ecotoxicity
No data were found.

7.17.2.8.3 Degradation/Treatment
Due to its inorganic nature and relative inactivity, TiC is not expected to be readily degraded.

7.18 Tin [Sn], tin monoxide [SnO], and tin dioxide [SnO_2]

7.18.1 General Information
Tin is a soft, white, silvery metal that is insoluble in water but soluble in acid or alkali. It is used to line cans for food, beverages, and aerosols, and is present in brass, bronze, pewter, and some soldering materials. The ATSDR has published a Toxicological Profile for tin and its compounds (ATSDR 2005b).

Tin dioxide is a white or slightly gray crystalline solid. Synonyms include dioxotin, flowers of tin, stannic anhydride, stannic dioxide, stannic oxide, tin(IV) oxide and tin peroxide (HSDB 2005f).

7.18.2 Toxicology Data

7.18.2.1 Oral
Elemental tin is generally considered of low oral toxicity due to poor gastric absorption. Results of animal experiments indicate that ingestion of considerable amounts of powdered tin may cause vomiting but not permanent injury (HSDB 2005f).

The ATSDR has established a Minimal Risk Level (MRL) of 0.3 mg/kg-day for an intermediate duration (15–364 days) oral exposure to inorganic tin (based on $SnCl_2$), which includes both elemental tin and inorganic tin compounds and is much more readily absorbed than elemental tin (ATSDR 2005b).

The acute LD_{50} for oral administration of SnO_2 to rats and mice is reported to be greater than 20 g/kg (PubChem 2017a).

Rats fed tin dioxide in their feed for 4–13 weeks showed no effects at levels up to 1% (HSDB 2005f).

7.18.2.2 Inhalation
Exposure to dust or fumes is known to cause a benign pneumoconiosis (stannosis). This form of pneumoconiosis produces distinctive progressive x-ray changes of the lung as long as exposure persists, but there are no distinctive fibrosis, no evidence of disability, and no special complicating factors (HSDB 2005f, ATSDR 2005b).

Exposure to fumes or dust of tin dioxide can result in stannosis, a mild pneumoconiosis, typically after 3–5 years of exposure. Fibrosis of the lung does not develop unless other agents such as silica are present (HSDB 2005f).

Inhalation of tin dioxide is classified in the GHS as Category 3, based upon information provided to the European Chemical Agency (ECHA) by commercial firms, indicating potential respiratory

irritation (PubChem 2017a).

7.18.2.3 Dermal
Contact with inorganic tin salts produces mild irritation of the skin and mucous membranes, but no systematic studies are available (ATSDR 2005b).

Use of tin dioxide as a component of cosmetics at levels of 0.4% for rinse-off products and 1.3% for leave-on products was found to be safe by the Cosmetic Ingredient Review Expert Panel. Tin dioxide is a water-insoluble product and, therefore, should not be absorbed percutaneously. Systemic exposure is unlikely (Johnson et al. 2014).

7.18.2.4 Ocular
Tin dust is an ocular irritant (HSDB 2005f).

No data were found for SnO_2. Due to its crystalline solid structure, tin dioxide can be assumed to be an ocular irritant.

7.18.2.5 Development and Reproduction
No data were found for any tin compounds.

7.18.2.6 Genotoxicity
No data were found for any tin compounds.

7.18.2.7 Carcinogenicity
Elemental tin causes nonspecific smooth surface carcinogenesis in experimental animals where small tin disks are implanted subcutaneously or intramuscularly (HSDB 2005f).

There is no evidence that the tin compounds are carcinogenic in humans.

7.18.2.8 Ecotoxicology

7.18.2.8.1 Fate and Transport
No data were found. Elemental tin is not expected to be mobile in the environment.

7.18.2.8.2 Ecotoxicity
Van Vleet (1982) found that feeding tin(II) chloride at 1000 mg/kg to ducklings receiving a Se-Vitamin E-sufficient diet was sufficient to induce Se-Vitamin E deficiency.

The LC_{50} for exposure of *Hyalella azteca* in water from Lake Ontario to elemental tin was greater than 1000 µ/L, the highest dose measured in the system investigated (Borgmann et al. 2005).

Due to its insolubility, tin dioxide is expected to be immobile in the environment. If released to the atmosphere, it is expected to exist primarily in particulate form. Partition to the atmosphere is not expected due to its physical nature. The International Chemical Safety Card (ICSC) indicates bioaccumulation may occur in crustaceans (NIOSH 2016); however, no confirmation of this statement has been found. Due to its insolubility, tin dioxide is generally not expected to

bioaccumulate.

7.18.2.8.3 Degradation and Treatment

As an element, tin is not subject to degradation but may engage in reactions to produce various tin ions.

7.19 Cobalt [Co], cobalt(II) oxide [CoO], and cobalt(II/III) oxide [Co_3O_4]

7.19.1 General Information

Cobalt is a silvery, grey solid metal. Elemental cobalt is chemically stable in water but can be oxidized to cobalt ions by action of nitric acid, hydrochloric acid, or sulfuric acid (Budavari 1996).

CoO is a black to green crystalline solid. Synonyms include cobalt monoxide, oxocobalt, Zaffre, cobaltous oxide, and monocobalt oxide (PubChem 2017b). Cobalt(II,III) oxide is a black crystalline solid that transforms to CoO at temperatures of 900–950°C (Weast 1978). It is also known as cobalt(2+); cobalt(3+); oxygen(2-) (its IUPAC name); cobaltosic oxide; cobalt tetraoxide; tricobalt tetraoxide; cobaltic-cobaltous oxide; and cobalto-cobaltic tetraoxide (PubChem 2017c).

7.19.2 Toxicology Data

Cobalt is an essential element as it is a cofactor for vitamin B12; however, excessive exposure produces goiter and reduced thyroid activity. Exposure to cobalt alone produces an allergic contact dermatitis and occupational asthma (Barceloux 1999). Systemic toxicity, including cardiac effects from cobalt exposure, has been noted in cases of degradation of cobalt-containing prostheses, such as hip joints. Effects have also been noted on the thyroid (hypothyroidism) and white blood cell proliferation (polycythemia) prior to cardiac effects (Packer 2016).

7.19.2.1 Oral

Cobalt is available for oral ingestion in the form of over-the-counter nutritional supplements. Tvermoes et al. (2014) studied the effect of ingesting 1.0 mg/day of a commercially available cobalt supplement over a 3-month period by human volunteers. After 90 days of dosing, mean cobalt blood concentrations were lower in men than in women, with mean blood/serum concentrations in men being about 20 µg/L and in women 53 µg/L. Estimated red blood cell cobalt concentrations suggest cobalt was sequestered in red cells during their 120-day life span, resulting in slower whole blood clearance when compared to serum. Renal clearance of cobalt increased with serum concentration and was, on average, lower in women (3.5 mL/min) compared to men (5.5 mL/min). Gender-specific differences were observed in cobalt absorption and excretion. There were no clinically significant changes in biochemical, hematologic, or clinical variables.

The oral LD_{50} for CoO in rats has been reported as 202 mg/kg (PubChem 2017b). Aggregated GHS information from 19 notifications provided to the ECHA by 355 companies rated oral ingestion of CoO as GHS Category 3 or 4. No data were cited (PubChem 2017b).

Less than 0.5% of CoO given orally to hamsters at a dose of 5 mg is absorbed (PubChem 2017b).

No data were found for Co_3O_4.

7.19.2.2 Inhalation

Symptoms of cobalt overexposure include cough, difficulty breathing, wheezing, decreased pulmonary function, weight loss, dermatitis, diffuse nodular fibrosis, respiratory hypersensitivity, and asthma (NIOSH 2016).

Inhalation and dermal exposure to cobalt particles can result in sensitization. Bronchial asthma has been described in workers exposed to various forms of cobalt. Interstitial lung disease caused by cobalt particles is an occupational lung disease generally referred to as “hard metal lung disease” (HSDB 2006b).

Workers occupationally exposed to airborne concentrations of cobalt from 0.8 to 1.2 mg/m^3 reported nausea, abdominal pains, loss of appetite, cough, and a deterioration of their sense of smell. A small number had decreased hemoglobin levels and red blood cell counts; liver and spleen enlargement; and dermatitis (HSDB 2006b).

Aggregated GHS information from 19 notifications provided to the ECHA by 355 companies rated inhalation effects of CoO as GHS Category 1 or 2 for toxicity, and Category 1, 1A, or 1B for respiratory sensitization and breathing difficulties (PubChem 2017b).

Studies on hamsters indicate about 1/3 of inhaled cobalt is absorbed. Twenty-four hours after inhalation of 0.8 mg of cobalt oxide, 23% was recovered in the carcass, 3% in the lung, and 0.5% in the liver and kidney together. Of the inhaled amount, 60% was recovered in the gastrointestinal (GI) tract. The amount of cobalt recovered in the GI was possibly cleared from the lung since GI excretion of parenterally administered cobalt is comparably low. Conversely, studies in rats show that the pulmonary absorption of inhaled CoO may be considerably less. Intratracheally instilled CoO (1.5 µg) was retained in the lung for a relatively long period with a half-time of about 15 days, indicating pulmonary absorption of CoO is a slow process (PubChem 2017b).

Aggregated GHS information from 36 notifications provided to the ECHA by 800 companies identified Co_3O_4 as a Category 1, 1A, or 1B inhalation hazard due to respiratory sensitization leading to allergy or asthma symptoms (PubChem 2017b).

7.19.2.3 Dermal

Inhalation and dermal exposure to cobalt particles can result in sensitization. Dermal exposure is mildly irritating (HSDB 2006b).

Larese Filon et al. (2004) demonstrated that when dispersed in synthetic sweat, cobalt powder is capable of permeating human skin at a rate of 0.0123 $µg/cm^2$-hour, with a lag time of 1.55 hours.

Aggregated GHS information from 19 notifications provided to the ECHA by 355 companies rated dermal effects of CoO as GHS Category 1 for skin sensitization (PubChem 2017b).

Aggregated GHS information from 36 notifications provided to the ECHA by 800 companies identified Co_3O_4 as a Category 1 skin sensitizer (PubChem 2017b).

7.19.2.4 Ocular

Cobalt dust is mildly irritating to the eyes (HSDB 2006b).

Ocular exposure to CoO can result in redness and pain (PubChem 2017b).

7.19.2.5 Development and Reproduction

Cobalt was embryotoxic to rat fetuses when administered during the entire period of gestation at a dose of 0.05 mg/kg. Cobalt can adversely affect spermatogenesis and accessory sex organ function (HSDB 2006b).

No data were found for Co_3O_4.

7.19.2.6 Neurotoxicity

Catalani et al. (2012) reviewed neurotoxicity of cobalt on the basis of high levels of cobalt released from metal prostheses (e.g., artificial hips). Some patients presented with tinnitus, deafness, vertigo, visual changes, optic atrophy, tremor, and peripheral neuropathy. The authors hypothesize these effects are due to individual susceptibility due to altered metal-binding proteins, altered transport processes in target cells, or polymorphic variation of genetic background.

A wide range of cognitive-behavioral sequelae, including memory deficits, result from hard metal disease in humans. Rats exposed to cobalt demonstrated decreased exploratory behavior and a trend for higher-dose subjects to show decreased passive avoidance learning. No significant differences in active maze learning were found (Czarnota et al. 1998).

7.19.2.7 Genotoxicity

Cobalt in combination with various metal carbides was evaluated in the comet and micronucleus assays. In the micronucleus test, cobalt induced a statistically significant concentration-dependent increase in micronucleated binucleates. Less definitive results were obtained with the comet assay (DeBoeck et al. 2003).

Kirkland et al. (2014) performed studies according to Organization for Economic Cooperation and Development (OECD)-recommended protocols in an attempt to resolve inconsistencies among results in several systems commonly used to assess genotoxicity. Both soluble and poorly-soluble cobalt compounds were tested. Induction of chromosomal damage was confirmed *in vitro*; however, this appeared to be due to oxidative stress. No biologically significant mutagenic responses were obtained in bacteria, Tk(+/-), or Hprt mutation tests. Negative results were also obtained for chromosomal aberrations (in bone marrow or spermatogonia) and micronuclei at maximum tolerated doses *in vivo*. Poorly soluble cobalt compounds do not appear to be genotoxic. Soluble compounds do induce some DNA and chromosomal damage *in vitro*, probably due to reactive oxygen. The absence of chromosome damage in robust Good Laboratory Practice studies *in vivo* suggests effective protective processes are sufficient to prevent oxidative DNA damage in whole mammals. The authors

conclude that overall there is no evidence of genetic toxicity of relevance for humans from cobalt substances or cobalt metal.

7.19.2.8 Carcinogenicity

There is inadequate evidence of carcinogenicity of cobalt and cobalt compounds in humans. In experimental animals, there is sufficient evidence of carcinogenicity for cobalt metal powder, and limited evidence for metal alloys containing cobalt. There is sufficient evidence for the carcinogenicity of cobalt(II) oxide in experimental animals (HSDB 2006c).

Aggregated GHS information from 36 notifications provided to the ECHA by 800 companies identified Co_3O_4 as a Category 1A, 1B carcinogen (PubChem 2017c).

Numerous research papers have investigated the effects of Co_3O_4 nanoparticles in cell culture systems, revealing the mode of action is likely generation of reactive oxygen species (ROS) that cause damage to cellular DNA (Rajiv et al 2016, Uboldi et al. 2016, Mao et al. 1996, Leonard et al. 1998).

Behl et al. (2015) reported on two chronic inhalation studies conduct by the NTP in rats and mice; one used soluble cobalt sulfate hexahydrate, and the other used elemental cobalt. Both compounds were found to be genotoxic in *Salmonella* T98 strain in the absence of effects on micronuclei. The major sites of toxicity and carcinogenicity in both studies were the respiratory tracts in rats and mice, and the adrenal gland in rats. In addition, there were distinct sites of toxicity and carcinogenicity noted following exposure to elemental cobalt. In rats, carcinogenicity was observed in the blood, pancreas, and testes. In mice, effects were seen in the testes only. The study concluded that both forms of cobalt are multi-site rodent carcinogens following inhalation exposure.

7.19.2.9 Ecotoxicology

7.19.2.9.1 Fate and Transport

Due to its insolubility, elemental cobalt is expected to be immobile in the environment. However, with weathering, solubilization to Co(II) species is likely to occur.

Beak et al. (2011) studied speciation and distribution of cobalt species in soils after the addition of Co(II) to the soil. In the aging and submerged-drying cycling studies, cobalt was found to be associated with the manganese and iron oxide fractions, with some of the cobalt being oxidized to the +3 state. The surface speciation suggests an innersphere complex was present in both cases. *In vivo* rice root box experiments showed similar cobalt speciation in the manganese oxide fraction; however, the iron oxide was unimportant in cobalt retention. A significant amount of the cobalt in the root box experiments was identified as a cobalt precipitate. This study confirms earlier macroscopic work that manganese oxides are important in the sequestration of cobalt in soils, and the presence of roots needs to be taken into account when addressing cobalt speciation.

Lee and Tebo (1994) found that marine bacteria of the *Bacillus* strain SG-1 that are known to oxidize Mn(II) to Mn(III) were also capable of oxidizing Co(II) to Co(III). Oxidation of cobalt did not occur in the absence of oxygen, indicating the mechanism did not involve abiotic chemical

reaction.

Jeffree et al. (2014) sampled bony bream (*Nematalosa erebi*) and black catfish (*Neosilurus ater*) from fresh surface waters of the Finniss River in northern Australia along a metal pollution gradient draining the Rum Jungle copper/uranium mine, a contaminant source for more than 50 years. Paradoxically, population of both fish species exposed to the highest concentration of mine-related metals (Co, Cu, Pb, Mn, Ni, U, and Zn) in surface water had the lowest tissue concentrations of these metals. The degree of reduction in tissue concentrations was also specific to each metal and inversely related to its environmental increase above background. Geochemical speciation modeling of metal bioavailability showed no differences between contaminated regions and control sites. The macro-nutrients (Ca, Mg, and Na) were not elevated with trace metal contamination. Reduced contamination exposure due to avoidance behavior was also unlikely. The authors felt the most plausible explanation to be modified kinetics of metal bioaccumulation physiology to reduce body burden of metals.

7.19.2.9.2 Ecotoxicity

Aggregated GHS information from 19 notifications provided to the ECHA by 355 companies rated the inhalation effects of CoO as GHS Category I for aquatic toxicity with long-lasting effects (PubChem 2017b).

Porukhabbaz et al. (2011) exposed a freshwater fish, *Capoeta fusca*, to $CoCl_2$ for 96 hours at two different levels of water hardness: 130 mg/L and 350 mg/L as $CaCO_3$, respectively. Water hardness had a significant effect on toxicity, with LC_{50} values for Co of 91.7 mg/L at the lower hardness level and 127.2 mg/L at the higher.

Aggregated GHS information from 36 notifications provided to the ECHA by 800 companies identified Co_3O_4 as hazardous to aquatic life or the environment, but the categorizations ranged from I to III, and no data were cited (PubChem 2017b).

7.19.2.9.3 Degradation/Treatment

With weathering, elemental cobalt is expected to be oxidized to Co(II) species that will be mobile in the environment.

7.20 Boron oxide [B_2O_3]

7.20.1 General Information

Boron oxide exists as colorless, brittle, vitreous, semitransparent, hygroscopic lumps or hard white crystals (Budavari 1996). Synonyms include boron trioxide, boric anhydride, diboron trioxide, boron sesquioxide, boric acid anhydride and oxo(oxoboranyloxy)borane.

7.20.2 Toxicology Data

Potential symptoms of overexposure are nasal irritation, conjunctivitis, and erythema (Budavari 1996).

7.20.2.1 Oral

In humans, the minimum lethal dose of ingested boron (as boric acid) is reported to be 2–3 g in infants, 5–6 g in children, and 15–20 g in adults. However, a review of 784 human poisonings

with boric acid (10–88 g) reported no fatalities, with 88% of cases being asymptomatic. Liver, kidney, CNS, and gastrointestinal effects and skin lesions have been found in lethal cases following ingestion of boron, but death has been attributed to respiratory failure (ATSDR 2010). Acute-duration oral exposures of human to high levels of boron (as boric acid) have resulted in little or no observable toxicity. In accidental poisonings of up to 88 g, 88% of the cases were asymptomatic. However, gastrointestinal, cardiovascular, hepatic, renal, CNS effects, dermatitis, erythema, and death have been observed in children and adults exposed to more than 84 g B/kg (ATSDR 2010).

The LD_{50} in mice is reported to be 3,163 mg/kg (HSDB 2006d).

7.20.2.2 Inhalation

B_2O_3 is a respiratory irritant (Budavari 1996).

7.20.2.3 Dermal

Skin effects can occur following ingestion of or dermal exposure to boron (as boric acid) in humans. Alopecia occurred on the heads of three automobile mechanics dermally exposed to boric acid or borax (ATSDR 2010). B_2O_3 is a dermal irritant and can cause erythema (Budavari 1996).

Application of 1 g of boric oxide dust to a 25 cm^2 area of skin on 4 rabbits produced erythema for 2–3 days (HSDB 2006d).

7.20.2.4 Ocular

Boric acid dust is mildly irritating to the eyes (HSDB 2006d).

7.20.2.5 Development and Reproduction

Aggregated GHS information from 17 notifications provided to ECHA by 424 companies classify B_2O_3 as a reproductive toxicant in GHS Category 1A or 1B (PubChem 2017e).

Duydu et al. (2016) investigated the reproductive effects of boric acid in humans in comparison to animals. The GHS classification of boric acid is Category 1B, based upon the reproductive effects of boric acid and sodium borate in animal experiments at high doses. However, boron reproductive effects have not been demonstrated to date in epidemiological studies. An epidemiological study at the Bandirma boric acid production plant tested 204 male workers. Sperm quality parameters (sperm morphology, concentration, and motility parameters), follicle-stimlulating hormone (FSH), luteinizing hormone (LH), and testosterone levels were determined in all participating employees. Unfavorable effects on reproduction were not found, even under very high daily boron exposures (0.21 mg/kg-day) conditions. The NOAEL for rat reproductive toxicity is equivalent to a boron blood level of 2,020 ng/g. This level is higher than the mean blood boron concentration (223.89 ng/g) of the high-exposure-group workers by a factor of 9. The authors suggest the classification be lowered to Category 2, with advisory H3621d (suspected of damaging the unborn child).

A study of 28 male boric acid production workers occupationally exposed to 22–80 mg/m^3 boron aerosols (boron form uncertain) for more than 10 years revealed low sperm counts, reduced

sperm motility, and elevated fructose content of seminal fluids compared to controls. These effects are consistent with high-dose animal exposures. However this study is limited by the small number of subjects and limited data reporting. Furthermore, a cross-sectional survey of 753 employees working for at least 9 months at a borax production facility in California found worker fertility rates to be higher than the U.S. national average; this study is limited by lack of exposure data (ATSDR 2010).

El-Dakdoky and Abd El-Wahab (2013) reported on a study where adult male rats were treated orally with boric acid for a period of 60 days at dosages of 0, 125, 250, and 500 mg/kg-day. The 125 mg/kg-day dose had no adverse effects on fertility, sperm characteristics, or prenatal development of the impregnated females. However, at 250 mg/kg-day, serum nitric oxide, testosterone, estradiol, and testicular boron and calcium levels were significantly increased, and serum arginase, sperm quality, and testicular DNA content were significantly reduced. DNA fragmentation was also observed. At 250 mg/kg-day, there was an increase in pre-implantation loss with a resulting decrease in live fetuses/litters. At the 500 mg/kg-day dose, testicular atrophy was observed, with severe damage to spermatogenesis; spermiation failure; and significant reduction of Mg and Zn levels in the testes. None of the male rats at the 500 mg/kg-day level could impregnate untreated females, indicating a loss of fertility, most likely by decreasing DNA synthesis rate rather than induction of DNA damage.

A NOAEL of 30 mg B/kg-day was identified for reproductive effects (testicular atrophy) in males in a 3-generation rat study (ATSDR 2010).

7.20.2.6 Neurotoxicity

Case reports in humans, primarily infants, indicate that neurological effects occur after ingestion of boron at high dose levels. Degenerative changes in brain cells, perivascular hemorrhage, and intravascular thrombosis have been reported in fatal case reports in infants, but neurochemical or neurophysiological changes have not been reported (Wong et al. 1964, Settimi et al. 1982).

7.20.2.7 Genotoxicity

In vitro genotoxicity tests have given generally negative results for boron. Negative results were obtained in the Ames test using *Salmonella typhimurium* and *E. coli* with or without microsomal activation, and in human lymphocytes, mouse embryo fibroblasts, mouse lymphoma, human foresking fibroblast, and CHO cells. Human lymphocytes tested positive for chromosomal aberrations (ATSDR 2010).

7.20.2.8 Carcinogenicity

The IARC, NTP, and EPA have not classified boron as a human carcinogen (ATSDR 2010). In an epidemiological study in Texas, the boric acid level in groundwater was found to correlate with a decrease in the incidence of prostate cancer. Boric acid was also found to improve the anti-proliferative effectiveness of the chemoprotective agents selenomethionine and genistein while enhancing ionizing radiation cell kill in a cell culture system (Barranco et al. 2007).

7.20.2.9 Ecotoxicology

7.20.2.9.1 Fate and Transport

Boron is generally found in nature bound to oxygen and never found as a free element. Boric

oxide is readily soluble in water and is expected to be moderately mobile if released to soil or water. In the presence of water, boric oxide is transformed to boric acid. Mobility and adsorption of boric oxide will be dependent upon the pH of the water and character of the soil. Greatest adsorption is generally observed at pH 7.5–9.0; the amount of adsorption in soil is dependent upon the amount of aluminum oxide present (ATSDR 2010).

Boric oxide is not expected to partition to the atmosphere from water or wet or dry soil and will exist in the atmosphere primarily as a particulate or aerosol. Boric oxide will be readily removed from the atmosphere by wet or dry deposition (ATSDR 2010).

It is unlikely that boric oxide is bioconcentrated significantly by organisms from water (ATSDR 2010).

7.20.2.9.2 Ecotoxicity

The 48-hour EC_{50} tested as boric acid in *Daphnia magna* is 370–490 mg/L. Boric oxide, the anhydrous form of boric acid, is equivalent to 1.776 parts of boric acid in aqueous solution. In fish, various LC_{50}s were determined as follows: Goldfish (*Carassius auratus*), 570 mg/L/3 days, 150 mg/L/7 days; Channel catfish (*Ictalurus punctatus*), 710 mg/L/5 days, 500 mg/L/9 days; Largemouth bass (*Micropterus salmoides*), 300 mg/L/8 days; and Rainbow trout (*Salmo gairdneri*), 480 mg/L/24 days, 320 mg/L/28 days (HSDB 2006a).

Physiological effects were noted in waterweed (*Elodea Canadensis*) after a 21-day static exposure at 2000 µg/L (ECOTOX 2017).

Esim et al. (2013) subjected 11- and 15-day-old maize seedlings to 2 or 4 mM boron in the form of boric acid for 2 or 6 days. At the end of the treatment period, root length, hydrogen peroxide content, malondialdehyde content, and the antioxidant enzymes superoxide dismutase, peroxidase, and catalase were measured. Excess boron was found to negatively affect root length and antioxidant enzyme activity. Peroxide and malondialdehyde levels were seriously affected by boron.

Boron is an essential element in plants (ATSDR 2010).

7.20.2.9.3 Degradation/Treatment

Boron is not significantly removed during conventional treatment of waste water. Boron may, however, be co-precipitated with aluminum, silicon, or iron to form hydroborate compounds (ATSDR 2010).

7.21 Antimony(III) oxide [Sb_2O_3]

7.21.1 General Information

Antimony(III) oxide is a white, odorless crystalline powder. It is also known as antimony(3+), oxygen(2-)(IUPAC name), senarmontite, antimonious oxide, antimony white, valentinite, and white star, among others (PubChem 2017d).

7.21.2 Toxicology Data

7.21.2.1 Oral
The oral LD_{50} in the rat is reported to be greater than 34.6 g/kg (HSDB 2013).

Ingestion of Sb_2O_3 causes irritation of the mouth, nose, stomach and intestines; vomiting; purging with bloody stool; slow pulse; low blood pressure; slow, shallow breathing; coma; and convulsions sometimes followed by death (HSDB 2013).

7.21.2.2 Inhalation
Inhalation of Sb_2O_3 causes inflammation of the upper and lower respiratory tract, including pneumonitis (HSDB 2013).

7.21.2.3 Dermal
Contact of Sb_2O_3 with skin causes dermatitis and rhinitis (HSDB 2013).

7.21.2.4 Ocular
Contact of Sb_2O_3 with the eyes causes conjunctivitis (HSDB 2013).

7.21.2.5 Development and Reproduction
Women workers exposed in an antimony plant experienced a greater incidence of spontaneous abortions than did a control group of unexposed working women. There were higher rates of spontaneous late abortions (12.5 vs. 4.1%), premature births (3.4 vs. 1.2%), and gynecologic problems (77.5 vs. 56%) among female metallurgical workers exposed to antimony aerosols. Antimony concentrations were not specified, but air samples reportedly contained metallic dust, antimony trioxide, and antimony pentasulfide. Weights of the offspring began to lag behind those of control babies at 3 months and were significantly reduced at 1 year. Blood antimony levels were 10 times those of a corresponding unexposed group of women, and average urinary antimony levels ranged from 2.1 to 2.9 mg percent vs. none detected in the controls. Antimony was also measured in breast milk, placental tissue, amniotic fluid, and the umbilical cord (HSDB 2013).

Conveyance of antimony in breast milk has been demonstrated (HSDB 2013).

7.21.2.6 Genotoxicity
Cavallo et al. (2002) studied genotoxicity in occupationally exposed workers employed in application of fire retardant chemicals. Sister chromatid exchange (SCE), micronucleus, and comet tests were employed. Of the two groups evaluated, the more exposed group showed more oxidative damage in the comet assay than the less-exposed group. No difference was found between the two groups in the SCE or micronucleus tests. The authors asserted these results are supportive of an oxidative damage to DNA mode of action for antimony genotoxicity.

Elliot et al. (1998) reported results from several genotoxicity assays employing antimony trioxide. Negative results were obtained in the Ames *Salmonella* test and the L5178Y mutation assay, but a positive result was observed in the *in vitro* assay employing isolated peripheral human lymphocytes. *In vivo*, antimony trioxide was non-clastogenic in the mouse bone marrow micronucleus assay, following oral gavage administration for 1, 7, 14, or 21 days at doses up to 5000 mg/kg (single dose) or 1000 mg/kg (repeated dose). A negative result was also obtained in the *in vivo* rat liver DNA repair (unscheduled DNA synthesis) assay following a single oral

gavage administration of doses up to 5000 mg/kg. These data show no genotoxicity for antimony trioxide *in vivo* and do not confirm a previous report of clastogenicity in the mouse on repeated dosing. The authors concluded antimony trioxide is not genotoxic *in vivo* and does not present a genotoxic hazard to humans.

7.21.2.7 Carcinogenicity

The IARC indicates there is inadequate evidence for the carcinogenicity of antimony trioxide in humans. There is sufficient evidence for carcinogenicity in experimental animals. The ACGIH classifies antimony trioxide as a probable human carcinogen (HSDB 2013).

7.21.2.8 Ecotoxicology

7.21.2.8.1 Fate and Transport

If released to soil or water, antimony trioxide is not expected to be mobile in the environment, due to low solubility and absence of vapor pressure. Antimony trioxide is not expected to partition to the atmosphere from wet soil or water. If released to the atmosphere, antimony trioxide is expected to exist primarily in particulate form. Antimony trioxide is not likely to bioaccumulate due to insolubility.

7.21.2.8.2 Ecotoxicity

The 48-hour EC_{50} for green algae (*Pseudokirchneriella subcapitata*) is reported to be 740 µg/L (ECOTOX 2017).

The 48-hour EC_{50} for *Daphnia magna* is reported to be 423.4 mg/L, and for a 24-hour exposure, 555.3 mg/L. The LC_{50} in bluegill sunfish (*Lepomis macrochirus*) is reported to exceed 530 mg/L for a 96-hour exposure and in fathead minnow (*Pimephales promelas*) to be greater than 833 mg/L for a 96-hour exposure (HSDB 20013).

Ainsworth et al. (1991) studied uptake and retention of antimony in the short-tailed vole, as previous studies had indicated elevated organ concentrations of antimony. Antimony trioxide in the diet produced elevated organ concentrations, but even after 60 days of observation, no harmful effects were evident. An equilibrium between uptake and excretion of antimony seemed to be rapidly established, and progressive increases in organ concentrations did not occur. When dietary intake was terminated, antimony was rapidly cleared. Comparison of findings from the laboratory and the field suggest inhalation was an additional route of intake in the field. The authors concluded that present levels of antimony are unlikely to cause toxic effects in the wild population.

The fate and toxicity of antimony trioxide in soil has been studied by Oorts et al. (2008). A silt-loam soil (pH 7.0, background 0.005 mmol Sb/kg) was amended with antimony trioxide at various concentrations. More than 70 percent of the antimony in the soil was present as Sb(V) within 2 days. The soil solution Sb concentrations in freshly-amended $SbCl_3$ (more soluble than Sb_2O_3) after 7 days equilibration were equivalent to those in Sb_2O_3-amended soils after 5 years. Data indicated that Sb solubility in this soil was controlled by a combination of sorption on the soil surface, Sb precipitation at higher doses, and slow dissolution of Sb_2O_3, the latter being modelled with a half-life between 50 and 250 days. Toxicity of Sb to plant growth (root elongation of barley, shoot biomass of lettuce) or to nitrification was found in soil equilibrated

with Sb_2O_3 (up to 82 mmol Sb/kg) for 31 weeks with 10 percent inhibition values at soil solution Sb concentrations of 110 µM Sb or above. These concentrations are equivalent to 4.2 mmol Sb/kg soil (510 mg Sb/kg) at complete dissolution of Sb_2O_3 in this soil. No toxicity to plant growth or nitrification was evident in toxicity tests starting one week after soil amendment with Sb_2O_3, whereas clear toxicity was found in a similar test using $SbCl_3$. However, these effects were confounded by a decrease in pH and an increase in salinity. It is concluded that the Sb(V) toxicity thresholds are over 100-fold larger than background concentrations in soil and that care must be taken to interpret toxicity data of soluble Sb(III) forms due to confounding factors.

7.21.2.8.3 Degradation/Treatment

As an inorganic compound, antimony trioxide is not readily subject to degradation. However, biological transformation of antimony oxides may be possible, as oxidation of antimony trioxide by the bacterium *Stitobacter senarmontii*, an autotrophic bacterium isolated from antimony ores, has been demonstrated (HSDB 2013).

7.22 Aluminum [Al] and aluminum oxide [alumina, Al_2O_3]

7.22.1 General Information

In pure form, aluminum is a white, ductile metal. Aluminum is readily oxidized and does not appear in pure form in nature, but most commonly as the silicate or oxide (O'Neil 2006).

While a considerable body of knowledge exists about aluminum and its salts, the most important forms under consideration for explosives, propellants, and pyrotechnics are elemental aluminum (CASRN: 7429-90-5) and its oxidation product, aluminum oxide, also known as alumina (CASRN: 11092-32-3; 1344-28-1). Nano-aluminum has also been of increasing interest as an energetic booster in explosives, propellants, and pyrotechnics. According to the ATSDR (2008), with the exception of aluminum phosphide, the anionic component of aluminum salts does not appear to influence toxicity, although it does appear to influence bioavailability.

The oxide is a hard, white powder also known as alumina. Alumina is an electrical insulator and is insoluble in water but very hygroscopic (Budavari 1996). As with any metallic compound, the aluminum ion is subject to oxidation and reduction in the environment, in humans, or in other animals, so the speciation and substitution of the aluminum ion can be variable.

7.22.2 Toxicology Data

The hypothesis that aluminum might be involved in the development of Alzheimer's Disease was first advanced in the 1980s (Perl and Moalem 2006) and has remained a subject of investigation to the present (Bondy 2010, Bharathi et al 2008, as well as many others).

7.22.2.1 Oral

No oral LD_{50} value for aluminum has been established. Aluminum-containing food additives are Generally Recognized As Safe (GRAS) by the U.S. Food and Drug Administration (ATSDR 2008). Persons with normal kidney function who use aluminum-containing medications can ingest much larger amounts of aluminum than in the diet. Possibly as much as 12–71 mg Al/kg-day can be ingested from antacid/anti-ulcer products, and 2–10 mg Al/kg-day from buffered analgesics, when taken at recommended dosages (Lione 1985).

Aluminum causes death in laboratory animals only at doses that are high compared to normal human exposure. Because animals can be exposed to large amounts of aluminum through their diets, dose rates must be computed carefully and are often underestimated (ATSDR 2008). LD_{50} values of 261 and 286 mg Al/kg-day (as the nitrate salt) have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al. 1987). For aluminum chloride, LD_{50} values of 370, 222, and 770 mg Al/kg-day have been reported for Sprague-Dawley rats, Swiss Webster mice, and male Dobra Voda mice, respectively (Llobet et al. 1987; Ondreicka et al. 1966).

Mortality occurred in female Swiss Webster mice exposed to aluminum lactate for 42 days throughout gestation and lactation at doses of 184 or 280 mg Al/kg-day (Golub et al. 1987) but not at 330 mg Al/kg-day in a different study by the same group of investigators (Donald et al. 1989). This apparent contradiction was attributed to shortcomings in the animals' diet in the first study. When several essential nutrients, particularly calcium, magnesium, and phosphate, were restored to the diet, survivability of the test animals improved. Only one of 9 pregnant Swiss Webster mice receiving 250 mg Al/kg-day as aluminum lactate failed to survive (Golub et al. 1987). No mortality was observed in male Sprague-Dawley rats receiving 70 mg Al/kg-day as aluminum chloride in water for 30, 60, or 90 days (Dixon et al. 1979), or up to 158 mg Al/kg-day as aluminum hydroxide in feed for 16 days (Greger and Donnaubauer 1986). These doses do not reflect aluminum consumed as part of the base diet (ATSDR 2008).

Al accumulates in erythrocytes and causes toxicity to the erythrocyte membrane. Rats were intragastrically exposed to 0, 64 (1/20 LD_{50}), 128 (1/10 LD_{50}), or 256 (1/5 LD_{50}) mg/kg $AlCl_3$ in double distilled water for 120 days. At the 120-day point, the systolic and mean arterial blood pressure, osmotic fragility, percentage of membrane proteins, activities of Na/K-ATPase, Mg^{2+}-ATPase, Ca^{2+}-ATPase, catalase, superoxide dismutase and glutathione peroxidase enzymes were determined, as well as malondialdehyde content of the erythrocyte membrane. Results showed that $AlCl_3$ elevated the systolic and mean arterial blood pressure, increased osmotic fragility, decreased the percentage of membrane protein, inhibited the measured enzyme activities, and increased the malondialdehyde content of the erythrocyte membrane. These results indicate $AlCl_3$ may induce hypertension by disturbing the function of the erythrocyte membrane (Zhang et al. 2016).

Acute toxicity of alumina is rare. Most cases of aluminum toxicity in humans are from one of two categories: patients with chronic renal failure, or people exposed to aluminum in the workplace. Aluminum inhibits bone remodeling, causing osteomalacia. It is believe to inhibit erythropoiesis, causing anemia. Insoluble aluminum compounds are poorly absorbed (HSDB 2008c).

7.22.2.3 Inhalation

While there are no systematic studies in humans, several deaths have been reported after occupational exposure to a finely powdered metallic aluminum used in paints, explosives, and fireworks (Mitchell et al. 1961). A 19-year old male working in an atmosphere heavily contaminated with aluminum (615–685 mg Al/m^3; respirable dust 51 mg Al/m^3) developed dyspnea (difficulty breathing) after 2.5 years. His symptoms grew worse, and he had to stop working after an additional 3 months; he died 8 months later. Of 27 workers in this plant, 2 died and 4 had radiological changes on x-rays.

McLaughlin et al. (1962) described the death of a male exposed to aluminum flake powder. Prior to death, the man exhibited memory loss, speech difficulties, convulsions, weakness, electroencephalogram (EEG) abnormalities, dysarthria (speech difficulties), hemiparesis (paralysis on one side of the body), and slowed reactions. However, neurological symptoms were not found in 53 other workers at the factory, and renal problems may have contributed to fatality in this case.

Of the experiments performed in animals, none has shown death from inhalation exposure to aluminum or its compounds. For example, no deaths were reported following an acute 4-hour exposure to up to 1,000 mg/m^3 as aluminum oxide in groups of 12–18 male Fischer 344 rats (Thomson et al. 1986). At about 30 mg/m^3, alveolar wall thickening and increased number of macrophages were consistent observations in the Golden Syrian hamster (33 mg/m^3 aluminum chlorhydrate 3 hours/day for 3 days; and the New Zealand rabbit (43 mg/m^3 aluminum chlorhydrate 4 hours/day for 5 days (Drew et al. 1974).

Respiratory effects typically associated with inhalation of particulates and lung overload have been observed in animals. The pulmonary toxicity of alchlor, a propylene glycol complex of aluminum chlorhydrate that is a common component of antiperspirants, was examined in hamsters in a series of studies (Drew et al. 1974). Three-day inhalation exposure to 31 or 33 mg Al/m^3 resulted in moderate-to-marked thickening of the alveolar walls due to neutrophil and macrophage infiltration and small granulomatous foci at the bronchioloalveolar junction. A decrease in the severity of the pulmonary effects was observed in animals killed 3, 6, 10, or 27 days after exposure termination.

No death occurred following chronic exposure to 2.18 or 2.45 mg/m^3 as refractory alumina fiber for 86 weeks in groups of 50 male and female Wistar rats (Pigott et al. 1981). At 5.1 mg/m^3 aluminum chlorhydrate 6 hours/day, 5 days/week for 24 months in the Fischer 344 rat, a 108–274% increase in lung-to-body weight ratio was observed, due mostly to the 16–26 percent decrease in body weight (Stone et al. 1979). Following the same dosing regimen, a 21% increase in lung-to-body weight ratio was observed in guinea pigs (Stone et al. 1979).

Workers chronically exposed to aluminum-containing dusts or fumes have developed severe pulmonary reactions, including fibrosis, emphysema, and pneumothorax. A much rarer encephalopathy has also been described (HSDB 2008c).

7.22.2.4 Dermal

Application of aluminum compounds to the skin, such as found in cosmetics, may cause rashes in some people. Skin damage has been observed in mice, rabbits, and pigs exposed to aluminum chloride or aluminum nitrate but not following exposure to aluminum sulfate, aluminum hydroxide, aluminum acetate, or aluminum chlorhydrate (ATSDR 2008).

Skin rashes were common symptoms reported by 48 people in England who consumed drinking water containing unknown levels of aluminum sulfate for approximately 5 days; however, the results are conflicted due to elevated levels of copper and lead in the water (ATSDR 2008).

No systematic data were found. Al_2O_3 is not considered to be a dermal irritant.

7.22.2.5 Ocular

Although information is limited, aluminum compounds have not shown any tendency to cause ocular irritation (Nair et al. 2002, Allemandi et al. 1999, Gettings et al. 1992). Particulate aluminum could potentially cause irritation on the basis of particle size rather than chemical composition.

Exposure to dust may cause minor irritation to the eyes (HSDB 2011b).

7.22.2.6 Development and Reproduction

Reproductive toxicity caused by Al via generation of free radicals is reportedly reduced by administration of coenzyme Q10 (CoQ10) and fish oil (Mohammad et al. 2015). Fifty male rats were gavaged with either 1% gum acacia (control group) or $AlCl_3$ (34 mg/kg-day) for 10 weeks. Concurrently, $AlCl_3$-treated rats received no treatment, CoQ10 (10 mg/kg-day orally), and/or fish oil (400 mg/kg-day) for 10 weeks. $AlCl_3$ caused a significant decrease in serum testosterone, LH, and FSH, as well as in testicular weight, antioxidant enzyme gene expression and activities, glutathione, zinc, cyclic adenosine-3',5'-phosphate (cAMP) contents, and the number of Leydig cells. Also noted were down-regulation of 3-β-hydroxysteroid dehydrogenase (3βHSD), 17βHSD, steroidogenic acute regulatory protein (STAR), and cholesterol side-chain cleavage enzyme (P450scc) gene expression. However, testicular Al, malondialdehyde, and nitric oxide levels were markedly increased. Treatment with CoQ10 and fish oil, alone or in combination, led to an improvement in these biomarkers. CoQ10 seems to be more effective than fish oil regarding oxidative and nitrosative stress, Zn deficiency, and Al overload. However, fish oil showed more pronounced effects than CoQ10 on hormones, steroidogenic markers, and cAMP. A cocktail of both demonstrated greater protective effects on testicular tissue than monotherapy.

The only human data on developmental effects comes from infants with renal failure and premature infants, both of whose responses are probably not indicative of responses in normal infants. Conditions observed in impaired infants were osteomalacia and increased bone and serum levels of aluminum in infants with kidney failure receiving more than 100 mg Al/kg-day as aluminum hydroxide from the first or sixth month of life, and in healthy infants ingesting aluminum-containing antacids. Progressive encephalopathy was also observed among children with severe renal disease ingesting aluminum-containing phosphate binders (ATSDR 2008).

In rats and mice, a variety of effects have been found including decreased pup survival/increased pup mortality, decreased growth, delayed maturation, and impaired neurodevelopment. These effects were seen in animals receiving 155 mg Al/kg-day or more delivered to the dam on gestational days 8–20, or on post-natal days 5–14. Interpretation of these data is usually hindered by lack of data on the aluminum content of the diet. Gestational exposure to aluminum does not appear to result in an increase in the occurrence of malformations and anomalies, although reductions in ossification have been observed. Animal studies provide strong evidence that gestational or lactational exposure to aluminum impairs development of the nervous system, and exposure to aluminum has consistently resulted in observation of decreased forelimb and /or hindlimb grip strength (ATSDR 2008).

Aluminum in drinking water has been linked to CNS birth defects. Some aluminum compounds have proven teratogenic in laboratory animals; however, overall, aluminum is not considered teratogenic (HSDB 2011c).

7.22.2.7 Neurotoxicity

Aluminum is a neurotoxin although the basis for its toxicity is unknown. It has recently been shown to alter the function of the blood-brain barrier. Aluminum increases the rate of transmembrane diffusion and selectively changes saturable transport systems without disrupting the integrity of the membranes or altering CNS hemodynamics. Such alterations in the access to the brain of nutrients, hormones, toxins, and drugs could be the basis of CNS disfunction (Banks and Kastin 1989).

Subtle neurological effects have been observed in workers chronically exposed to aluminum dust or fumes. These effects include impaired performance on neurobehavioral tests and increased reporting of subjective neurological symptoms (ATSDR 2008). As noted above, aluminum exposure has been postulated to play a role in the development of Alzheimer's Disease.

Dementias are associated with a relative insufficiency of magnesium in the brain. Such insufficiency may be attributable to low intake or retention of magnesium or high intake of a neurotoxic metal into brain tissue. Glick (1990) proposed that Alzheimer's Disease involves a defective transport process characterized by both an abnormally high incorporation of aluminum and abnormally low incorporation of magnesium into brain neurons. The hypothesis is advanced that an altered serum protein contributes to the progression of Alzheimer's Disease by having a greater affinity for aluminum than magnesium. The altered protein is proposed to cross the blood-brain barrier more efficiently than the normal protein and competes with the normal protein in binding to brain neurons.

7.22.2.8 Genotoxicity

Although aluminum complexes with DNA, particularly at lower pH levels, *in vitro* assays are nearly uniformly negative, to include Ames testing in *S. typhimurium*, DNA damage in *E. coli*, the rec assay in *B. subtilis*, forward mutation in the thymidine kinase locus of L5178Y mouse lymphoma cells, and morphological transformation in Syrian hamster cells. However, other studies have indicated aluminum can induce DNA cross-linking in rat ascites hepatoma cells, micronuclei formation in human peripheral blood lymphocytes, and chromosome aberrations in human peripheral blood lymphocytes (ATSDR 2008).

Aluminum oxide is negative in the Ames *Salmonella typhimurium* test with or without metabolic activation. Negative results are also obtained in the *Bacillus subtilis* recombination assay and in *in vivo* assays (HSDB 2011b).

7.22.2.9 Carcinogenicity

A number of human studies have examined the occurrence of cancer among aluminum industry workers and found a higher-than-expected cancer mortality rate, but this is probably due to the other potent carcinogens to which they are exposed, such as polynuclear aromatic hydrocarbons (PAH) and tobacco smoke. The International Agency for Research on Cancer (IARC) concluded that aluminum production was carcinogenic to humans and that pitch volatiles

have fairly consistently been suggested in epidemiological studies as being possible causative agents. The EPA and U.S. Department of Health and Human Services (DHHS) have not evaluated the human carcinogenic potential of aluminum (ATSDR 2008).

Significantly increased incidences of gross tumors were reported for Long Evans rats (males) and Swiss mice (females) given 0.6 or 1.2 mg/kg-day aluminum potassium sulfate in drinking water, for 2–2.5 years (Schroeder & Mitchener 1975a, 1975b). The incidence of "lymphoma leukemia" was significantly increased (10/41 vs. 3/47 in controls) in the female mice. A dose-response relationship could not be determined for either species because only one aluminum dose was used, and the types of tumors and the organs in which they were found were not specified. Another study in Wistar rats found no increase in the incidence of neoplasms in male and female rats fed diets containing unspecified amounts of aluminum phosphide/ammonium carbamate for 24 months (Hackenberg 1972). The incidence of spontaneous hepatocellular carcinoma in B6C3F1 mice that ingested ≤979 mg/kg-day aluminum potassium sulfate for 20 months was significantly decreased in the high-dose males (5.5 percent compared to 20.5 percent in controls; Oneda et al. 1994). In summary, no mammalian studies have found any conclusive evidence for carcinogenicity of aluminum. Also, the DHHS and the EPA have not yet evaluated the human carcinogenic potential of aluminum.

7.22.2.10 Ecotoxicology

7.22.2.10.1 Fate and Transport

Metallic aluminum is insoluble in water; the solubility of the oxide and other compounds depends upon the pH and salinity of the soil, and the availability of anions or ligands with which the aluminum can form complexes. In general, the mobility of aluminum in soil is greatest when the soil is rich in organic matter capable of forming aluminum-organic complexes and when the pH is low, such as areas prone to acid rain or in acidic mine tailings (ATSDR 2008).

Aluminum oxide is generally considered insoluble in water but is capable of dissolving slowly, especially at non-neutral pH. The rate of dissolution is so slow, however, that aluminum does not pose a hazard for groundwater transport. Migration in soil or groundwater is likely to be retarded by adsorption to soil components. There is no tendency for aluminum oxide to partition between water or wet soil and the atmosphere. Any aluminum oxide present in the atmosphere will be present in particulate form. Aluminum oxide is not expected to bioconcentrate in aquatic species.

7.22.2.10.2 Ecotoxicity

Available data suggest that aluminum is low in toxicity. Many aquatic species have been used in toxicity assays, as have many forms of aluminum, including oxides (ECOTOX 2017). Terrestrial plants and animals have also shown relatively low toxicity associated with aluminum, but a significant reduction in pH may cause an increase in bioavailability and toxicity as a consequence (ATSDR 2008).

Khangarot (1991) exposed tubifex worms (*Tubifex tubifex [Muller]*) to aluminum ammonium bis(sulfate) dodecahydrate in water. The EC_{50} values were 69.82 mg/L for 24 hours, 55.85 mg/L for 48 hours, and 50.23 mg/L for 96 hours.

Plant species and cultivars of the same species differ considerably in their ability to take up and translocate aluminum to above-ground parts. Tea leaves may contain very high concentrations of aluminum. Other plants that may contain high levels of aluminum include *Lycopodium*, *Symplocos*, *Orites,* and a few ferns. Aluminum is often taken up and concentrated in root tissue. It is unclear to what extent aluminum is taken up into root food crops and leafy vegetables; however, it is clear that aluminum is not bioconcentrated in plants (ATSDR 2008).

Aluminum is not bioaccumulated to a significant degree in most fish and shellfish (ATSDR 2008).

Reduced abundance was found for green algae (*Chlorella sp*.) at a concentration of 1.00 g alumina/L. No data were found for *Daphnia*. Mortality was found in Zebrafish (*Danio rerio*) 5 days post-fertilization a 20.0 mg/L (ECOTOX 2017).

The LOEL for Duckweed (*Lemna minor*) was found to be 10 mg alumina/L after 7 days and 3 doses (ECOTOX 2017).

7.22.2.10.3 Degradation/Treatment

As an element, aluminum is not subject to environmental degradation, but it can form compounds with other elements. The most common form of aluminum in the environment is alumina, Al_2O_3; other forms of aluminum may be present depending upon the pH.

As an inorganic compound, aluminum oxide is not subject to degradation in the manner of organic compounds. However, the aluminum ion can exchange anionic species and become a different substance.

7.23 Ammonium dihydrogen phosphate [NH_4][H_2PO_4]

7.23.1 General Information

Ammonium dihydrogen phosphate is a white crystalline powder that is stable in air. Uses include preparation of buffer solutions and pH control, as baking powder with sodium bicarbonate, in fermentation, and in fireproofing of paper, wood and fiberboard. Ammonium dihydrogen phosphate will dissociate in water to produce an ammonium ion (pKa = 9.25) and the dihydrogen phosphate anion (pKa2 = 7.20 and pKa3 = 11.9); a 0.2 M aqueous solution has a pH of 4.2. Synonyms include ammonium phosphate monobasic, ammonium biphosphate, and primary ammonium phosphate (O'Neil 2006).

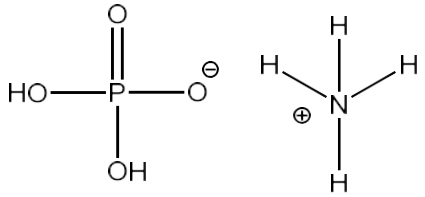

Figure 2. [NH_4][H_2PO_4]

7.23.2 Toxicology Data

7.23.2.1 Oral
No data on acute or chronic oral toxicity effects were found.

7.23.2.2 Inhalation
According to a manufacturer SDS, $[NH_4][H_2PO_4]$ is classified under the GHS as Category 3 for short term organ toxicity, since it may cause respiratory irritation if inhaled as the dry compound (Fisher Scientific 2012).

7.23.2.3 Dermal
According to a manufacturer SDS, $[NH_4][H_2PO_4]$ is classified under the GHS as Category 2 for skin irritation (Fisher Scientific 2012).

7.23.2.4 Ocular
According to a manufacturer SDS, $NH_4H_2PO_4$ is classified under the GHS as Category 2A for severe eye irritation (Fisher Scientific 2012).

7.23.2.5 Development and Reproduction
No data on developmental or reproductive effects were found.

7.23.2.6 Genotoxicity
No data were found. $[NH_4][H_2PO_4]$ is not expected to be mutagenic.

7.23.2.7 Carcinogenesis
No data were found. $[NH_4][H_2PO_4]$ is not expected to be carcinogenic.

7.23.2.8 Ecotoxicology

7.23.2.8.1 Fate and Transport
Due to its high solubility, $[NH_4][H_2PO_4]$ is expected to be highly mobile in groundwater. Partition to the atmosphere from water or wet surfaces is not anticipated due to the salt nature of the compound. Any $[NH_4][H_2PO_4]$ present in the atmosphere would be in particulate form (as aqueous droplets). $[NH_4][H_2PO_4]$ is also not expected to bioaccumulate due to its very high solubility.

7.23.2.8.2 Ecotoxicity
Aquatic ecotoxicity data for ammonium hydrogen phosphate was found only for the diatom *Amphora coffeaeformis*, where a decrease in population was noted at 1.0 to 5.0 mg/L (ECOTOX 2017).

ECOTOX (2017) also reports effects on the tomato (*Solanum lycopersicum* var. *lycopersicum*) at 300 mg/kg soil after a 28-day exposure (NOEL), and a NOEL of 2.6 mM (299 mg/L).

No other experimental data could be found, and computational predictions are not possible due to the inorganic nature of the compound.

7.23.2.8.3 Degradation/Treatment
$[NH_4][H_2PO_4]$ is not subject to mineralization, but may dissociate into its component cations and anions. Removal by wastewater treatment is expected to be poor in the absence of ion exchange scrubbing.

7.24 Aluminum silicate [Al_2SiO_5]

7.24.1 General Information
Synonyms for this substance include tetraaluminum;dioxido(oxo)silane;oxygen(2-) (IUPAC name); hexaaluminum pentaoxide disilicate; aluminum silicon oxide; mullite and aluminum oxide silicate; silicic acid, aluminum salt (1:6). Commercial applications include as dry toner for electrostatic latent image developer, and in the manufacture of anthroquinones and other chemical substances (PubChem 2017f).

Aluminum silicate is a constituent of synthetic vitreous fibers, which are inorganic materials that contain aluminum or calcium silicates and are made from rock, clay, slag, or glass. Different from natural mineral fibers (e.g. asbestos), synthetic vitreous fibers do not have a crystalline molecular structure (HSDB 2005h). Different forms of aluminum silicate are listed under multiple CAS RNs.

7.24.2 Toxicology Data
Most available information on aluminum silicate materials is based upon analysis of spun glass fibers, notably “refractory ceramic fibers.”

7.24.2.1 Oral
No data were found.

7.24.2.2 Inhalation
The inhalation LC_{50} in rats for a 4-hour exposure is reported to be greater than 2.19 mg/L (Sigma-Aldrich 2015a).

7.24.2.3 Dermal
Aluminum silicate is reported to not be a skin sensitizer (Sigma-Aldrich 2015a).

7.24.2.4 Ocular
Aluminum silicate is expected to be a mild ocular irritant due to its particulate nature.

7.24.2.5 Development and Reproduction
No data were found.

7.24.2.6 Genotoxicity
Aluminum silicate is reported to be negative in the Ames assay (Sigma-Aldrich 2015a).

7.24.2.7 Carcinogenesis
Aluminum silicate is classified as a likely human carcinogen based upon sufficient animal data but insufficient human data. Carcinogenicity in animal models occurs primarily via inhalation, but intraperitoneal/intrapleural injection or intratracheal instillation also caused peritoneal/pleural

mesotheliomas or lung tumors in rats and hamsters (IRIS 1993).

Five to ten intratracheal instillations of 6 mg of 0.01–0.03 µm particles given before week 26 of a 107–108 week study were admininstered to female Wistar rats. Treatment resulted in multiple tumors, including bronchio-alveolar carcinomas, bronchio-alveolar adenomas, squamous cell carcinomas, cystic keratinizing epitheliomas, and non-keratinizing epitheliomas (CCRIS 2008).

7.24.2.8 Ecotoxicology

7.24.2.8.1 Fate and Transport
Due to their insolubility, aluminum silicates are not expected to be mobile in the environment. If released to the air, mobility will depend upon local weather conditions and the size and nature of the particles. Bioaccumulation is not anticipated due to general insolubility.

7.24.2.8.2 Ecotoxicity
Growth inhibition (EC_{50}) for blue-green algae (*Anacystis aeruginosa*) and green algae (*Chlorella vulgaris*) have been reported in the range of 180–320 mg/L and 560–1,000 mg/L, respectively, for a 4-day exposure. The 48-hour LC_{50} for *Daphnia magna* in a static system ranged from 1,000–1,800 mg/L. Growth inhibition of Indian Catfish (*Heteropneustes fossilis*) for a 35–120 day exposure occurred at 20–50 mg/L, and the LC_{50}s for a 4-day exposure in guppy (*Poecilia reticulata*) and Japanese medaka (*Oryzias latipes*) were 1,800–3,200 mg/L and 3,200–5,600 mg/L, respectively (ECOTOX 2017).

7.24.2.8.3 Degradation/Treatment
Aluminum silicates are not expected to be subject to environmental degradation.

7.25 Strontium molybdate [$SrMoO_4$]

7.25.1 General Information
Strontium molybdate is a white, crystalline powder that is nearly insoluble in water. At temperatures above its melting point, it decomposes with loss of MoO_3 (AAA Molybdenum Products 2017). Its IUPAC name is strontium dioxido(dioxo)molybdenum. Synonyms include molybdate, strontium, and molybdenum strontium oxide. Molybdenum is an essential trace micronutrient element that plays an important role in animal and plant physiology. Molybdenum is a constituent of at least three mammalian metalloflavoproteins: xanthine oxidase, aldehyde oxidase, and sulphite oxidase (Eidi et al. 2011). Strontium exists in several isotopic forms. The naturally-occurring isotopes are ^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr. There is also a radioactive isotope, ^{90}Sr, that is only produced by nuclear explosions.

7.25.2 Toxicology Data
For strontium compounds, most data and the greatest hazard derive from the existence of a radioactive strontium isotope, ^{90}Sr. This profile will only address stable, non-radioactive strontium molybdate.

7.25.2.1 Oral
The most consistent effects of oral exposure to excess stable strontium are rickets and

osteomalacia, especially in the young (ATSDR 2004).

A LOAEL of 550 mg Sr/kg-day is identified for bone mineralization abnormalities in weanling rats exposed to dietary strontium carbonate for 20 days. The NOAEL for bone mineralization in weanling rats is 140 mg Sr/kg-day for an intermediate duration exposure. The NOAEL for adults is 690 mg Sr/kg-day (ATSDR 2004).

7.25.2.2 Inhalation
According to a supplier's SDS, strontium molybdate is classified in Category 3 of the GHS for specific organ toxicity to the respiratory system; it may cause respiratory irritation, but no supporting data were provided (Sigma-Aldrich 2016).

7.25.2.3 Dermal
According to a supplier's SDS, strontium molybdate is classified in Category 2 of the GHS for skin irritation, but no supporting data were provided (Sigma-Aldrich 2016).

7.25.2.4 Ocular
According to a supplier's SDS, strontium molybdate is classified in Category 2A of the GHS for ocular irritation, but no supporting data were provided (Sigma-Aldrich 2016).

7.25.2.5 Development and Reproduction
Sodium molybdate was orally administered to adult male rats at levels of 10, 30, and 50 mg/kg, 5 days per week, for 60 days. At higher dose levels, significant decrease in absolute and organ-to-body weight ratios of testes, epididymides, seminal vesicles, and ventral prostate was observed. Sperm abnormality, exhibited as a decrease in sperm motility and sperm count, was also observed. Significant decreases in the activities of the marker testicular enzyme sorbitol dehydrogenase, and increases in lactate dehydrogenase and ɣ-glutamyl transpeptidase, associated with histopathological changes in testes, were also observed. Accumulation of molybdenum in testes, epididymides, and seminal vesicles was also observed (Pandey and Singh 2002).

7.25.2.6 Genotoxicity
No data were found.

7.25.2.7 Carcinogenicity
No data were found.

7.25.2.8 Ecotoxicology

7.25.2.8.1 Fate and Transport
Due to insolubility, $SrMoO_4$ is not expected to be mobile in soil or groundwater. Lack of vapor pressure will prevent volatilization to the atmosphere, and only particulate material will be found in the air. Bioconcentration is not expected due to insolubility and lack of accumulation.

7.25.2.8.2 Ecotoxicity
Diamantino et al. (2000) studied acute and chronic effects of sodium molybdate (2000). An LC_{50} of 2,847.5 mg/L was determined for a 48-hour *Daphnia* exposure.

7.25.2.8.3 Degradation/Treatment
No data were found.

7.26 Strontium oxide [SrO]

7.26.1 General Information
Strontium exists in several isotopic forms. The naturally-occurring isotopes are ^{84}Sr, ^{86}Sr, ^{87}Sr, and ^{88}Sr. Its radioactive isotope, ^{90}Sr, is the product of nuclear explosions.

7.26.2 Toxicology Data
For strontium compounds, most data and the greatest hazard derive from the existence of a radioactive strontium isotope, ^{90}Sr. This discussion will only address stable, non-radioactive strontium molybdate.

7.26.2.1 Oral
In acute exposure studies in mice, the oral LD_{50} for strontium nitrate was reported to be 2,350 mg/kg in males (Llobet et al. 1991). For strontium chloride administered by gavage, the acute oral LD_{50} in mice was reported to be 2,900 mg Sr/kg for males and 2,700 mg Sr/kg in females (Ghosh et al.1990).

Storey (1961) fed young and adult rats diets supplemented with strontium carbonate at rates of 0.19, 0.38, 0.75, 1.0 (young rats only), 1.5, and 3.0% for 20 days. The basic diet contained sufficient calcium, phosphorous, and Vitamin D to support normal development. Based upon estimated food consumption, these dose rates corresponded to 95, 190, 375, 750, 1,000 (young rats only), 1,500, and 3,000 mg/kg-day. Test animals were evaluated for changes in bone mineralization and defects in cartilage. Young rats were more severely affected by reduced dietary strontium than adult rats. At 0.38% and lower, the epiphyseal plate was irregular and slightly wider; at 0.75%, measurements were irregular and unreliable. At doses >0.38%, inhibition of calcification was observed. In adults, the first obvious bone change occurred at 1.5% and included slightly wider than normal epiphyseal cartilage plate and metaphyseal osteoid seams. The cartilage plate was much wider in adult rats at the 3.0% feeding level. The NOAEL for young rats was 0.19% (190 mg/kg-day) strontium and was 0.75% (380 mg/kg-day) for adult rats. The LOAELs were 0.38% (288 mg/kg-day) for young rats, and 1.5% (750 mg/kg-day) for adults.

The premature death rate was 40% among weanling rats fed 565 mg Sr/kg-day for 43 days (Johnson et al. 1968). Marie and coworkers (1985) administered $SrCl_2$ to rats in their drinking water at rates of 0, 0.19, 0.27, 0.34, and 0.405 for a period of 9 weeks. Based upon water consumption, these concentrations were estimated to be dose rates of 0, 316, 425, 525, and 633 mg/kg-day. Doses lower than 0.40% (633 mg/kg-day) produced no effects on body growth or bone mineralization. At 0.40% and higher, there was increased mineralization lag time, excessive osteoid thickness associated with a decline in the rate of calcification and a slower growth rate, and a decreased double-labeled osteoid surface, frequently resulting in defective long bone growth. This study identified a NOAEL of 525 mg/kg-day and a LOAEL of 633 mg/kg-day.

Skoryna (1981) fed adult male RVH hooded rats $SrCl_2$ in their drinking water for 3 years at estimated dose rates of 70, 147, and 263 mg Sr/kg-day. No adverse effects were observed in any of the experimental animals. A chronic NOAEL of 263 mg Sr/kg-day was determined.

Chronic ingestion of more than 5 mg/kg-day is considered medically unacceptable for humans (HSDB 2003b). The EPA has established an oral reference dose for strontium (as $SrCO_3$) of 0.6 mg/kg-day (IRIS 2007). The ATSDR has set an oral exposure MRL for strontium at 2.0 mg/kg-day; there are insufficient data to establish an inhalation MRL (ATSDR 2004).

Ingested strontium concentrates in bone tissue, replacing the calcium in the bone matrix. Insufficient calcium intake, coupled with high levels of strontium absorption, can lead to poor bone development and rickets in growing children (ATSDR 2004).

7.26.2.2 Inhalation

The only information on inhalation toxicity of inhaled strontium nitrate involves a case of anaphalactic shock experienced by a female paramedic resulting from exposure to a roadside flare that contained approximately 75% strontium nitrate (Federman and Sachter 1997).

Experiments on inhalation poisoning of rats by strontium nitrate dust in concentrations of 44.6 ± 1.4 mg/m^3 for 4 hours daily for 1 month showed that strontium nitrate causes morphological and functional changes in the cardiovascular, hematopoetic, and nervous systems; in respiratory organs, the liver, and kidneys; and affects metabolism (Zyuzyukin 1974).

Studies conducted in animals have shown that the rate of absorption of strontium compounds is dependent upon the chemical form of the inspired strontium aerosol. Compounds of greater solubility are, in general, more rapidly cleared from the lung. Experimental clearance times range from 12 hours to 5 days, depending upon the solubility of the compound (ATSDR 2004).

7.26.2.3 Dermal

Strontium nitrate is highly irritating to the skin (HSDB 2003b).

7.26.2.4 Ocular

There is no indication that strontium nitrate causes long-term damage or irritation to eyes, but it is recommended that eyes be flushed for 15 minutes if exposed, which is a standard treatment. Use of safety glasses with side shields conforming to EN 166:2001 is recommended (Sigma-Aldrich 2010).

7.26.2.5 Development and Reproduction

There is no evidence to indicate strontium possesses any reproductive toxicity. Low levels of strontium salts appear to be beneficial to sperm (Mortimer 1986; Mortimer et al. 1986).

7.26.2.6 Genotoxicity

Oral administration of 130 mg Sr/kg as $SrCl_2$ to Swiss albino female mice increased the incidence of chromosomal aberrations in bone marrow cells 5-fold after 6 hours. Genotoxicity in male mice receiving the same dose was only doubled (Ghosh et al. 1990).

Mutagenesis assays using the Rec$^-$ strain of *Bacillus subtilis* indicated $SrCl_2$ did not induce mutations *in vitro* (Kanematsu, et al. 1980). Strontium was also found to have no adverse effect on the fidelity of DNA synthesis *in vitro* (Loeb et al. 1977).

7.26.2.7 Carcinogenicity

There is no information implicating non-radioactive ("stable") strontium in the development of cancer. Radioactive ^{90}Sr is a β^--emitter (0.546 MeV) with a half-life of 28.5 years; it is produced only as a consequence of nuclear reactions. Because strontium accumulates in bone, ^{90}Sr has been implicated in cancers of bone and the hematopoetic and immune systems (Bierke 1990).

7.26.2.8 Ecotoxicology

7.26.2.8.1 Fate and Transport

Strontium has moderate mobility in soils and sediments, and sorbs moderately to metal oxides and clays (Hayes and Traina 1998).

Several investigators have measured bioconcentration factors (BCF) of ^{90}Sr in both aquatic and terrestrial organisms (National Council on Radiation and Protection and Measurements (NCRP) 1984). Organisms with the highest uptake are aquatic organisms such as fish (largemouth bass), macroinvertebrates (insects), macrophytes (white-water lilies and bladderwort), and zooplankton. Because of the similarity of strontium to calcium, bony fish had a very high BCF; a value >50,000 was measured in bony tissue (Friday 1996).

Organisms such as fish generally bioaccumulate strontium with an inverse correlation to levels of calcium in water, but this correlation is not universal and does not apply to other organisms such as algae and plants (NCRP 1984).

7.26.2.8.2 Ecotoxicity

Erichsen-Jones (1936) tested the toxicity of strontium and several other metal ions to stickleback fish. The survival time for these fish was decreased at strontium levels above 1200 µg/L (roughly comparable to an LD_{LO} value).

7.26.2.8.3 Degradation/Treatment

No data were found. As Sr is an element, it is not subject to degradation but may enter into reactions with other species, thus altering its chemical form.

7.27 Strontium silicate [$SrSiO_3$]

7.27.1 General Information

Strontium silicate is an insoluble inorganic substance used in dental repair.

7.27.2 Toxicology Data

No significant toxicology information was found. When this compound is used as a dental cement, strontium ions may replace calcium in dental apatite, but this effect is without significant toxicological importance (Massera et al. 2015)

7.27.2.1 Oral
No data were found. Strontium silicate is insoluble and used in dental cements; it is not anticipated to be toxic.

7.27.2.2 Inhalation
No data were found.

7.27.2.3 Dermal
No data were found.

7.27.2.4 Ocular
No data were found.

7.27.2.5 Development and Reproduction
No data were found.

7.27.2.6 Genotoxicity
No data were found.

7.27.2.7 Carcinogenesis
No data were found.

7.27.2.8 Ecotoxicology

7.27.2.8.1 Fate and Transport
No data were found.

7.27.2.8.2 Ecotoxicity
No data were found.

7.27.2.8.3 Degradation/Treatment
No data were found.

7.28 Strontium aluminate [$SrAl_2O_4$]

7.28.1 General Information
As an inorganic salt, it is likely this compound is slightly non-stoichiometric in bulk form. The common name is strontium aluminate, and the IUPAC name is dialuminum strontium oxygen(2-).

7.28.2 Toxicology Data
Although there is virtually no toxicology information available for strontium aluminate, it is not believed to be a hazardous substance.

7.28.2.1 Oral
No data were found.

7.28.2.2 Inhalation
No data were found. Inhalation of dust should likely be avoided.

7.28.2.3 Dermal
No data were found.

7.28.2.4 Ocular
No data were found.

7.28.2.5 Development and Reproduction
No data were found.

7.28.2.6 Genotoxicity
No data were found.

7.28.2.7 Carcinogenicity
Strontium aluminate is not known to be carcinogenic (Sigma-Aldrich 2015b).

7.28.2.8 Ecotoxicology

7.28.2.8.1 Fate and Transport
Strontium aluminate is of a mineral nature, likely insoluble, and not likely to be mobile in the environment. Its bioaccumulation potential is believed to be low.

7.28.2.8.2 Ecotoxicity
No data were found.

7.28.2.8.3 Degradation/Treatment
No data were found. Due to its mineral nature, strontium aluminate is likely to resist degradation.

7.29 Molybdenum silicides [$MoSi_2$/Mo_5Si_3]

7.29.1 General Information
Molydenum silicide is a refractory ceramic with primary use in heating elements. It is also known as molybdenum disilicide.

7.29.2 Toxicology Data
Little toxicology information is available for molybdenum silicide. Based upon animal experiments, molybdenum and its compounds are highly toxic. Symptoms of acute poisoning include severe gastrointestinal irritation with diarrhea, coma, and death from heart failure. Experimental animals exposed to high levels accumulate molybdenum in the lungs, spleen, and heart, and showed a decrease of DNA and ribonucleic acid (RNA) in the liver, kidney, and spleen (ESPI 2007).

7.29.2.1 Oral
Ingestion may cause acute molybdenum poisoning (ESPI 2007).

7.29.2.2 Inhalation
May cause irritation to the upper respiratory tract and pneumoconiosis with chronic exposure (ESPI 2007).

7.29.2.3 Dermal
Prolonged or repeated contact may cause irritation (ESPI 2007).

7.29.2.4 Ocular
Prolonged or repeated contact may cause irritation (ESPI 2007).

7.29.2.5 Development and Reproduction
No data were found.

7.29.2.6 Genotoxicity
No data were found.

7.29.2.7 Carcinogenesis
No data were found.

7.29.2.8 Ecotoxicology

7.29.2.8.1 Fate and Transport
No data were found.

7.29.2.8.2 Ecotoxicity
No data were found.

7.29.2.8.3 Degradation/Treatment
No data were found.

8 Discussion

8.1 Compound Summaries

8.1.1 Manganese and its oxides [Mn, MnO, MnO_2, Mn_2O_3, Mn_3O_4]
Mn(0) is of low toxicity by all routes of exposure except inhalation. Repeated inhalation exposures may cause development of metal fume fever, a flu-like condition; or manganism, a Parkinson-like condition. MnO_2 also exhibits low systemic toxicity. Neurological symptoms may develop after oral ingestion via drinking water although evidence for these symptoms is more limited than for inhalation.

8.1.2 Silica [SiO_2]
Amorphous silica is essentially non-toxic unless transformed to a crystalline form by heating. Inhalation is the primary route of exposure. There is limited evidence of mutagenic properties for amorphous silica in some test systems; however, these are isolated and not anticipated to be generally characteristic of the material. Crystalline silica is a known human carcinogen, but the

incidence of the crystalline form in the material being used in this project is unknown at present.

8.1.3 Silicon [Si]

Silicon may exist in several crystalline forms in the solid state; some pose health hazards while others do not. Several of the different forms may be present simultaneously. During the combustion of silicon, the forms of silicon dioxide vapor that may be present are not readily apparent; however, both silicon and silica are relatively non-hazardous.

8.1.4 Bismuth oxide [Bi_2O_3]

Very little toxicity information is available for bismuth oxide, but its long history of use indicates it is nearly non-toxic by any route of exposure. Chronic consumption of bismuth salts can result in neurological effects, but this occurs only at high doses. There is some indication of possible mutagenicity resulting from inhalation of bismuth compounds, but there are no documented human consequences of mutagenicity.

Similarly, very little information exists for ecotoxicity. Due to its lack of solubility, bismuth oxide is not expected to pose an environmental hazard.

8.1.5 Red iron oxide [Fe_2O_3]

Iron compounds are ubiquitous in the environment and generally have few negative effects on living systems when present in low-to-moderate concentrations.

8.1.6 Black iron oxide [Fe_3O_4]

Iron compounds are ubiquitous in the environment and generally have few negative effects on living systems when present in low-to-moderate concentrations.

8.1.7 Tungsten [W], tungsten trioxide [WO_3] and manganese tungstate [$MnWO_4$]

Tungsten exhibits toxicity only as a fume in hard metal working or when oxidized to tungstate. Use of tungsten in a delay formulation is expected to cause formation of a lower oxide of tungsten (e.g., WO or WO_3) which could be oxidized to tungstate (WO_4^{2-}) upon weathering. Some occupational hazard may be present to the skin, eyes, and lungs, depending upon how the metal is worked during the production process. Leachate studies for tungsten oxidation products are recommended to determine the concentrations and kinetics of formation of possible ecotoxicants.

Inhalation is the primary route of exposure capable of causing potential human health problems. Tungsten compounds are generally believed to not pose a significant hazard via other routes of exposure.

$MnO\text{-}WO_4$ is of low toxicity except by inhalation, where extended exposure could possibly lead to neurological symptoms. The occupational hazard to skin and eyes is low, but standard chemical protective equipment should be employed, including respiratory protection. There is no information on developmental/ reproductive, genotoxic, or cancer hazard.

Ecotoxicity is likely low due to insolubility. High concentrations of manganese can inhibit the growth of plants. Effects on aquatic plants and terrestrial invertebrates are unknown.

8.1.8 Titanium [Ti]
Titanium is chemically inert and considered to be non-toxic.

8.1.9 Titanium hydride [TiH]
Significant toxicology gaps exist for TiH_2. While acute toxicity appears to be low, effects from chronic exposure are largely unknown. There appears to be a moderate hazard from occupational exposure that can probably be addressed through use of appropriate personal protective equipment. If human exposure is anticipated, testing is recommended for dermal irritation, dermal sensitization, ocular irritation, and inhalation toxicity.

8.1.10 Potassium nitrate [KNO_3]
Although there are few systematic toxicology studies of potassium nitrate, the compound is sufficiently well understood so that there are no exceptional toxicity concerns.

8.1.11 Zirconium [Zr]
Zirconium is considered to be essentially non-toxic, with ocular irritation the only known biological effect.

8.1.12 Polytetrafluoroethylene [PTFE]
Polytetrafluoroethylene is chemically and biologically inert and poses no toxicological hazard. Combustion and pyrolysis products are generally toxic via inhalation, and exposure should be avoided.

8.1.13 Titanium dioxide [TiO_2]
TiO_2 exhibits very low toxic hazard by any route of exposure other than inhalation. Inhaling TiO_2 particulates over an extended period of time could result in damage to the respiratory tract although cancer is unlikely in humans.

8.1.14 Titanium diboride [TiB_2]
Despite a lack of quantitative data, TiB_2 is reported to be low in toxicity (GHS Cat 4 for oral, inhalation, and dermal effects). Inhalation is judged to be the most hazardous route of exposure. Additional toxicological evaluation is desirable.

Ecotoxicity is reported to be low.

8.1.15 Titanium carbide [TiC]
TiC is a hard metal that represents an inhalation hazard only if present as a dust. No specific information on the effects of inhalation of TiC dusts was found.

Ecotoxicity of TiC is expected to be negligible.

8.1.16 Tin [Sn], tin monoxide [SnO], and tin dioxide [SnO_2]
Tin is a relatively non-toxic metal that causes gastrointestinal disturbance if ingested orally, and irritation if inhaled. Occupational health hazards are low, but precautions against inhalation should be taken. There are no data indicating tin is a developmental or reproductive toxicant, mutagen, or carcinogen. Ecotoxicity of elemental tin is likewise low, based on limited testing.

Tin dioxide is a substance of low overall toxicity. Inhalation for extended periods of time can result in stannosis, a mild form of pneumoconiosis, but the compound is otherwise without effect regardless of the route of exposure.

Ecotoxicity is also believed to be low due to the compound's insolubility.

8.1.17 Cobalt [Co], cobalt(II) oxide [CoO], and cobalt(II/III) oxide [Co_3O_4]

Although cobalt is an essential micronutrient in humans, it can be toxic via ingestion or inhalation. Cobalt oxides are also skin sensitizers. Many cobalt compounds exhibit genotoxicity not only in the Ames test but also in the micronucleus test; they exhibit clastogenic effects in human lymphocytes.

There are indications cobalt disturbs thyroid hormone production, resulting in increased thyroxine (T4) in the circulatory system. Systemic effects in man include peculiar vasodilation (flushing) of face and ears, mild hypotension, rash, tinnitus, and nerve deafness (HSDB 2006c).

8.1.18 Boron oxide [B_2O_3]

Boron oxide has low oral toxicity and is not mutagenic or carcinogenic. Dermal and ocular irritation effects are the most significant health effects. Boron compounds result in testicular atrophy in male laboratory animals but do not appear to have adverse effects on the fetus in humans.

Boron is an essential nutrient for plants; however, higher concentrations of boron can negatively impact plant growth. Toxicity toward aquatic invertebrate and animal species is low.

8.1.19 Antimony(III) oxide [Sb_2O_3]

Antimony trioxide exhibits low oral, inhalation, and developmental toxicity. Exposure can cause irritation to the skin and eyes. There are no significant indications of genotoxicity or carcinogenicity *in vivo*, although some *in vitro* systems and rodent test systems are positive.

Ecotoxicity is greatest for the lower trophic level organisms, possibly having an effect on sustainment of higher level organisms. The mobility of antimony trioxide in soil and groundwater is not expected to be significant due to the compound's low solubility.

8.1.20 Aluminum [Al] and aluminum oxide [Al_2O_3]

The toxicities of aluminum and its compounds are low overall and pose no acute toxicity risk to either humans or the environment. In the occupational health setting, however, precautions against inhalation of particulate aluminum or aluminum fumes are recommended due to documented cases of aluminum toxicity.

Aluminum oxide has uniformly low toxicity. The primary source of hazard is inhalation of particulates, usually in a work environment, but only moderate effects have been noted.

Aluminum oxide also appears to be of low toxicity in the environment.

8.1.21 Ammonium dihydrogen phosphate [NH_4][H_2PO_4]

[NH_4][H_2PO_4] is a common salt freely available in commerce and of generally low toxicity. Its physical form, i.e., dry solid or in solution, will determine the hazard of the material. When dissolved in water, [NH_4][H_2PO_4] will reduce the pH of water, but large quantities are required for detrimental effects to occur. The dry solid poses an irritation hazard via inhalation.

8.1.22 Aluminum silicate [Al_2SiO_5]

Because aluminum silicates exist in many diverse morphologies, generalizing their characteristics is difficult due to the likelihood of exceptions. However, these materials are generally non-toxic except via inhalation exposure, where they are primarily irritants. Laboratory animals exposed to inhaled aluminum silicates can develop cancer; however, this has not been seen in humans.

8.1.23 Strontium molybdate [$SrMoO_4$]

Significant data gaps exist for strontium molybdate. Acute oral toxicity appears to be moderate, but the compound poses an irritation hazard to the respiratory system, skin, and eyes. No data could be found relating to its genotoxicity or carcinogenicity. Studies in laboratory animals suggest a possibility of reproductive issues for males, with unknown consequences.

Ecotoxicity data were found for *Daphnia* only. Toxicity toward *Daphnia* is low. Due to the compound's insolubility, groundwater transport and bioaccumulation are unlikely.

8.1.24 Strontium oxide [SrO]

Strontium oxide is moderately toxic via oral ingestion, but there is no evidence of its ocular or developmental toxicity. Information on its inhalation toxicity in humans is lacking. There is limited evidence that SrO is genotoxic in laboratory rodents but no evidence that stable strontium compounds cause cancer. Ecotoxicity information is generally lacking, but the compound's toxicity toward fish is apparently moderate.

8.1.25 Strontium silicate [$SrSiO_3$]

No significant toxicology data were found. In the absence of inhalation exposure, strontium silicate is assessed to be of low toxicity.

8.1.26 Strontium aluminate [$SrAl_2O_4$]

No significant toxicology data were found. In the absence of inhalation exposure, strontium aluminate is assessed to be of low toxicity.

8.1.27 Molybdenum silicides [Mo_5Si_3 and $MoSi_2$]

Little toxicology information is available for molybdenum silicide. Molybdenum and its compounds are highly toxic based upon animal experiments. Symptoms of acute poisoning include severe gastrointestinal irritation with diarrhea, coma, and death from heart failure. Experimental animals exposed to high levels accumulate molybdenum in the lungs, spleen, and heart, and showed a decrease of DNA and RNA in the liver, kidney, and spleen (ESPI 2007).

8.2 Regulations and Standards

8.2.1 Manganese and its Oxides [Mn, MnO, MnO_2, Mn_2O_3, Mn_3O_4]

Manganese is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA). Disposal of waste Mn into water requires a discharge permit from the EPA, but disposal of manganese metal or compounds as solid waste is not regulated under current Federal law (ATSDR 2012).

8.2.1.1 Oral Exposure Criteria

Mn is designated as a hazardous substance in accordance with the Clean Water Act; the species of greatest concern is the MnO_4^- anion (ATSDR 2012). The EPA has established a Federal Drinking Water Guideline of 50 µg/L; higher guidelines have been established by Minnesota (300 µg/L); California, Connecticut, and Maine (500 µg/L); and New Hampshire (840 µg/L). New York State has established a Drinking Water Standard of 300 µg/L (HSDB 2008a, 2008b).

The EPA (IRIS 2011) derived an oral reference dose (RfD) value of 0.14 mg Mn/kg-day from all oral exposures.

For oral exposures, the ATSDR recommends an interim guidance level of 0.16 mg Mn/kg-day based on the Tolerable Upper Intake Level for adults of 11 mg Mn/day established by the Institute of Medicine (ATSDR 2012).

The World Health Organization (WHO 2011) drinking water quality guideline for manganese is 0.4 mg/mL (ATSDR 2012).

8.2.1.2 Inhalation Exposure Criteria

MRLs have been determined for manganese compounds. An MRL is defined as an estimate of human exposure to a substance that is likely to be without an appreciable risk of non-carcinogenic adverse effects over a specified period of exposure. The MRL for a chronic inhalation exposure of 365 days or more is set at 0.3 µg Mn/m^3 in respirable dust (ATSDR 2012).

The ACGIH has established an 8-hour time-weighted average (TWA) Threshold Limit Value (TLV) of 0.2 mg/m^3 (ATSDR 2012).

The NIOSH has established a Recommended Exposure Limit (REL) of 1 mg/m^3 for a time-weighted exposure and 3 mg/m^3 for a short-term exposure. The OSHA has established a Permissible Exposure Limit (PEL) of 5 mg/m^3. The immediately dangerous to life and health (IDLH) level is 500 mg/m^3, measured as manganese (IRIS 2011).

The EPA has established an MRL of 0.0003 mg Mn/m^3 in respirable dust on the basis of Benchmark Dose modeling and an oral RfD of 0.14 mg Mn/kg-day (ATSDR 2012).

Manganous oxide is listed as a hazardous air pollutant (HAP) in the Clean Air Act as amended in 1990.

The EPA derived a chronic inhalation reference concentration (RfC) of 5 x 10^{-5} mg/m^3 from a study of battery workers exposed to manganese dioxide (Roels et al. 1992).

The EPA (IRIS 2011) derived an RfD value of 0.14 mg Mn/kg-day from all oral exposures. The ACGIH has established an 8-hour TWA TLV of 0.2 mg/m^3 (ATSDR 2012).

The Federal Drinking Water Guideline for manganese is 50 µg/L; state standards are 300 µg/L in New York and Minnesota, and 500 µg/L in California, Connecticut and Maine (HSDB 2008a, 2008b).

8.2.2 Silica [SiO_2]

The NIOSH REL is a TWA of 6 mg/m^3, and the OSHA PEL is a TWA of 80 mg/m^3-%SiO_2 (NIOSH 2016).

8.2.3 Silicon [Si]

The OSHA PEL TWA is 15 mg/m^3 total dust, 5 mg/m^3 respirable fraction; the ACGIH TLV TWA is 10 mg/m^3 (ChemID*plus* 2013c, HSDB 2011).

8.2.4 Bismuth oxide [Bi_2O_3]

No regulations or standards were found for bismuth oxide.

8.2.5 Red iron oxide [Fe_2O_3]

The EPA has established a drinking water guideline for iron at 300 µg/L (HSDB 2012a). The OSHA has set a PEL at 10 mg/m^3 for an 8-hour TWA, and the ACGIH has set an 8-hour TWA at 5 mg/m^3 for the respirable fraction of particles.

8.2.6 Black iron oxide [Fe_3O_4]

The ACGIH has established a TWA TLV of 1 mg/m^3, measured as iron. The NIOSH has established a 10-hour TWA of 1 mg/m^3 for soluble iron salts, measured as iron (HSDB 2005b).

The EPA has established a Federal drinking water standard of 300 µg/L; state standards also exist for Illinois (1,000 µg/L), North Carolina (300 µg/L) and Maine (340 µg/L) (HSDB 2005b).

As a food additive, iron is Generally Recognized as Safe (GRAS, HSDB 2005b).

8.2.7 Tungsten [W], tungsten trioxide [WO_3] and manganese tungstate [$MnWO_4$]

The ACGIH has established an 8-hour TLV TWA of 3 mg/m^3 for tungsten and insoluble compounds (ACGIH 2018).

The ATSDR has not established oral or inhalation MRLs due to inadequate information (ATSDR 2005a).

The NIOSH REL for a 10-hour TWA exposure is 5 mg/m^3 (NIOSH 2016).

The OSHA has established a PEL of 5 mg Mn/m^3 (ESPI 2008).

8.2.8 Titanium
No regulations or standards pertaining to titanium were found.

8.2.9 Titanium hydride
The OSHA has established a PEL of 10 mg/m^3 for TiH_2; the ACGIH has adopted the same standard (ESPI 2005)

8.2.10 Potassium nitrate
The EPA has established an RfD for nitrates of 1.6 mg/kg-day on the basis of development of clinical signs of methemoglobinia (>10 percent) in infants 0–3 months old (HSDB 2007).

Potassium nitrate is approved as a component of rodenticides under the Federal Insecticide, Fungicide, and Rodenticide Act of 1972. Potassium nitrate is used as a curing agent for cod roe, and may not exceed 200 ppm in the finished roe. Drinking water standards exist at the Federal level, and in the states of Maine and Minnesota; all three standards are identical at 10,000 µg nitrate ion/L (HSDB 2007).

8.2.11 Zirconium
The NIOSH has established a TWA REL of 5 mg/m^3 for zirconium compounds; the OSHA PEL is identical. The IDLH limit for zirconium compounds, measured as Zr, is 25 mg/m^3 (NIOSH 2016).

8.2.12 Potassium nitrate [KNO_3]
No inhalation or ingestion standards have been established for potassium nitrate (NIOSH 2015).

8.2.13 Polytetrafluoroethylene [PTFE]
No regulations or standards pertaining to polytetrafluoroethylene were found.

8.2.14 Titanium dioxide [TiO_2]
The OSHA PEL is a TWA of 15 mg/m^3 (NIOSH 2016).

8.2.15 Titanium diboride [TiB_2]
TiB_2 is subject to Community Right-to-Know legislation in the states of Pennsylvania and New Jersey (Sigma-Aldrich 2014).

8.2.16 Titanium carbide [TiC]
No exposure limits have been established (ESPI 2015).

8.2.17 Tin [Sn], tin monoxide [SnO], and tin dioxide [SnO_2]
The ACGIH and NIOSH have established 8- and 10-hour TWA exposure limits of 2 mg/m^3 (ACGIH 2018). The IDLH level is 100 mg/m^3 measured as tin (HSDB 2005g). Minnesota has established a drinking water guideline of 4000 µg/L (HSDB 2005f).

The WHO permissible limit on tin in foods stored in tin-lined cans is 250 mg/kg (ATSDR 2005b).

8.2.18 Cobalt [Co], cobalt(II) oxide [CoO], and cobalt(II/III) oxide [Co_3O_4]

The NIOSH has established a REL of 0.05 mg/m^3 for a time-weighted 10-hour exposure. The inhalation IDLH level is 20 mg/m^3 (NIOSH 2016).

State drinking water standards for cobalt have been established by Arizona (0.70 µg/L) and Wisconsin (40 µg/L) (HSDB 2006).

8.2.19 Boron oxide [B_2O_3]

The OSHA has established an 8-hour TWA exposure limit of 15 mg/m^3. The NIOSH has established a 10-hour TWA exposure limit of 10 mg/m^3 (NIOSH 2016).

The ACGIH has established an 8-hour TWA TLV of 10 mg/m^3 (HSDB 2006d).

An MRL of 0.3 mg/m^3 has been derived for acute-duration inhalation exposures of 14 days or fewer to boron. This number was determined by using a NOAEL of 0.8 mg B/m^3 associated with a minimum LOAEL of 1.5 mg/m^3 for increased nasal secretions in exercising volunteers. The NOAEL was divided by an uncertainty factor of 3 to account for human pharmacodynamics response to boron (ATSDR 2010).

An MRL of 0.2 mg/kg-day has been derived for acute-duration (1–14 days) and intermediate duration (15–364 days) oral exposure to boron (ATSDR 2010).

The EPA has established a Federal drinking water guideline of 600 µg/L measured as boron. State limits are 630 µg/L in New Hampshire, 960 µg/L in Wisconsin, 1,000 µg/L in Minnesota and California, and 1,400 µg/L in Maine (HSDB 2006d).

8.2.20 Antimony(III) oxide [Sb_2O_3]

Both the NIOSH and OSHA have established time-weighted exposure limits of 0.5 mg/m^3 measured as antimony (NIOSH 2016).

Antimony trioxide is designated a hazardous substance under the Federal Water Pollution Control Act, and also regulated by the Clean Water Act Amendments of 1977 and 1978 (HSDB 2013).

The EPA has set a Maximum Contaminant Goal for antimony at 6 µg/L. State drinking water guidelines are 14 µg/L for Arizona, 6 µg/L for Minnesota, and 3 µg/L for Maine (HSDB 2013).

8.2.21 Aluminum [Al] and aluminum oxide [Al_2O_3]

Residues of aluminum oxide are exempt from the requirement for a tolerance when used as a diluent in accordance with good agricultural practices as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (HSDB 2011b).

The ACGIH has established a TLV of 1 mg/m^3 for an 8-hour exposure (ACGIH 2018). Excursions in exposure levels may exceed 3 times the TLV-TWA for no more than 30 minutes during a work day, but under no circumstances should exposure exceed 5 times the TLV-TWA (HSDB 2008c).

The EPA has established a Federal drinking water guideline of 50–200 µg/L. State guidelines are in effect for California (200 µg/L), Arizona (73 µg/L), and Maine (1430 µg/L); California has established a drinking water standard of 1,000 µg/L (HSDB 2008c).

The NIOSH (2017) has established a TWA REL of 10 mg/m^3 for total aluminum particulates, and 5 mg/m^3 for respirable particles. The OSHA PEL is 15 mg/m^3 with 5 mg/m^3 for respirable particles (NIOSH 2017).

The OSHA PEL is 15 mg/m^3 (total) with an 8-hour TWA of 5 mg/m^3 (respirable particles) (NIOSH 2017).

8.2.22 Ammonium dihydrogen phosphate [NH_4][H_2PO_4]

No regulations or standards pertaining to ammonium dihydrogen phosphate were found.

8.2.23 Aluminum silicate [Al_2SiO_5]

The ACGIH has established a time-weighted TLV of 1.0 mg/m^3 (Sigma-Aldrich 2015a). The NIOSH REL for kaolinite (hydrated aluminum silicate) is a TWA of 10 mg/m^3 for particulates and 5 mg/m^3 for respirable particles (NIOSH 2017).

“Mullite” is listed under the Right-to-Know laws of Pennsylvania and New Jersey (Sigma-Aldrich 2015a).

8.2.24 Strontium molybdate [$SrMoO_4$]

An MRL has been derived for intermediate-duration (15–364 days) oral exposure to stable strontium and its compounds (ATSDR 2004).

Strontium molybdate is listed under the Right-to-Know laws for the states of Pennsylvania and New Jersey (Sigma-Aldrich 2016).

8.2.25 Strontium oxide [SrO]

An MRL has been derived for intermediate-duration (15–364 days) oral exposure to stable strontium and its compounds (ATSDR 2004).

Several states have established limits on strontium in drinking water. A limit of 8 pCi/L of the radioactive isotope ^{90}Sr is in place in Alabama, California, Connecticut, Illinois, New Hampshire, and Wisconsin. Florida and Maine have established total strontium limits of 4,200 µg/L, and the EPA guideline is 4,000 µg/L.

8.2.26 Strontium silicate [$SrSiO_3$]

An MRL has been derived for intermediate-duration (15–364 days) oral exposure to stable strontium and its compounds (ATSDR 2004).

8.2.27 Strontium aluminate [$SrAl_2O_4$]

An MRL has been derived for intermediate-duration (15–364 days) oral exposure to stable strontium and its compounds (ATSDR 2004).

Strontium aluminate is listed in the Right-to-Know regulations for the states of Pennsylvania and New Jersey (Sigma-Aldrich 2015b).

8.2.28 Molybdenum silicide [$MoSi_2$/Mo_5Si_3]

The OSHA PEL and ACGIH TLV are reported to be 10 mg/m^3 measured as molybdenum (ESPI 2007).

8.3 Conclusions

The proposed formulation in the design configuration of the gasless delay fuze represents a low hazard to both human health and the environment. This fuze is intended to ignite the main charge of the munition after a period of delay to permit deployment of the munition (e.g., fragmentation or smoke grenade) without co-production of gaseous reaction products that would cause the container to rupture and release materials to the environment. Some of the reaction products produced represent inhalation hazards, but inhalation exposure is not expected to be a significant outcome in this application since there is no environmental release.

Exposure to the materials of the formulation is limited to manufacture and post-ignition degradation. As none of the materials pose a significant dermal contact hazard, occupational exposures are anticipated to be of low hazard. The munitions fragments that remain after the device function are likely to be released to the environment only through weathering. The human health and environmental effects of these released compounds are expected to be minimal because their groundwater transport potential is limited, the ultimate compounds are ubiquitous in the environment, and the chemicals released are generally considered low in toxicity.

Although there are some data gaps across the board for these substances (Table 4), the conditions of use (i.e., no significant inhalation exposure) for this item do not mandate that the gaps be filled at this time. Should these substances be present in other formulations where significant exposure, especially by inhalation, is a possibility, additional data collection would be desired.

This project is somewhat atypical since all of the constituent compounds are inorganic substances that have not had the number of deliberate/systematic toxicity testing studies that newly-developed organic compounds (e.g., pharmaceutical and agricultural chemicals) receive. Toxicity evaluation of inorganic chemicals is further complicated by the tendency of these substances to undergo oxidation-reduction reactions, both in the environment and within biological organisms. In some cases, product literature (often the only available source of

information) may assert that a substance has a defined toxicological endpoint but fail to provide supporting data, and such data cannot be found by regular literature search. In some cases, the only available information was anecdotal information that did not indicate the boundaries of the responses.

QSAR modeling cannot currently be carried out on inorganic materials.

9 Recommendations

There are no recommendations for additional toxicity data collection at this time since all of the combustion products are minerals common to soils and are of low toxicity. Should this formulation be used in applications where release to the environment is anticipated, a reassessment of the conclusions of this investigation would be required.

10 Point of Contact

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Appendix A

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Appendix B
Globally Harmonized System

"GHS" is the acronym for the Globally Harmonized System of Classification and Labeling of Chemicals. The GHS attempts to establish international consensus for defining health, physical, and environmental hazards of chemicals; creating a classification process for comparison with defined hazard criteria; and communicating hazard information and protective measures on labels and Safety Data Sheets (formerly known as Material Safety Data Sheets). The GHS attempts to reduce differences among levels of worker protection established by the different countries and reduce regulatory burden and barriers to commerce while establishing consistent standards for classification. The GHS is the result of an international mandate adopted in the 1992 United Conference on Environment and Development, often called the "Earth Summit." The harmonization and classification of chemicals was one of six program areas endorsed by the United Nations General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While the GHS comprises several aspects, the most important area for our purposes is the classification of chemicals into various hazard categories based upon their effects and route of exposure. Tables B-1 through B-4 present tabular extracts of the criteria for acute toxicity (both oral and inhalation), skin corrosion/irritation, ocular effects, and aquatic toxicity (both acute and chronic), respectively. More information can be found in the original source material (OSHA 2012).

Table B-1. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2000	Criteria: –Anticipated LD_{50} between 2000 and 5000 mg/kg –Indication of significant effects in humans –Any mortality in Category 4 –Significant clinical signs in Category 4 –Indications from other studies *If assignment to a more hazardous class is not warranted.
Dermal (mg/kg)	≤50	>50 ≤200	>200 ≤1000	>1000 ≤2000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2500	>2500 ≤5000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts & Mists (mg/L)	≤0.05	>0.05 ≤0.5	>0.5 ≤1.0	>1.0 ≤5	

Legend:
mg/kg = milligrams per kilogram
mg/L = milligrams per liter
ppm = parts per million

Table B-2. GHS Skin Corrosion/Irritation

Skin Corrosion Category 1			**Skin Irritation Category 2**	**Mild Skin Irritation Category 3**
Destruction of dermal tissue; visible necrosis in at least one animal.			Reversible adverse effects in dermal tissue Draize score: ≥2.3, <4.0, or persistent inflammation	Reversible adverse effects in dermal tissue Draize score: ≥1.5, <2.3
Subcategory 1A Exposure <3 minutes Observation <1 hour	Subcategory 1B Exposure <1 hour Observation <14 days	Subcategory 1C Exposure <4 hours Observation <14 days		

Table B-3. GHS Eye Effects

Category 1 **Serious Eye Damage**	**Category 2** **Eye Irritation**	
Irreversible damage 21 days after exposure Draize score: Corneal opacity ≥3 Iritis ≥1.5	Reversible adverse effects on cornea, iris, conjunctiva Draize score: Corneal opacity ≥1 Iritis >1 Redness ≥2 Chemosis ≥2	
	Irritant Subcategory 2A Reversible in 21 days	Mild irritant Subcategory 2B Reversible in 7 days

Table B-4. GHS Acute and Chronic Aquatic Toxicity

Acute Category I	**Acute Category II**	**Acute Category III**	
Acute toxicity ≤1.00 mg/L	Acute toxicity >1.00 but ≤10.0 mg/L	Acute toxicity >10.0 but <100 mg/L	
Chronic Category I	**Chronic Category II**	**Chronic Category III**	**Chronic Category IV**
Acute toxicity ≤1.00 mg/L and lack of rapid biodegradability and log Kow ≥4, unless BCF <500.	Acute toxicity >1.00 mg/L but ≤10.0 mg/L and lack of rapid biodegradability, and log Kow ≥4, unless BCF <500 and unless chronic toxicity >1 mg/L.	Acute toxicity >10.0 mg/L but ≤100.0 mg/L and lack of rapid biodegradability and log Kow ≥4, unless BCF <500 and unless chronic toxicity >1 mg/L.	Acute toxicity >100.0 mg/L and lack of rapid biodegradability and log Kow ≥4, unless BCF <500 and unless chronic toxicity >1 mg/L.

Legend:
BCF = bioconcentration factor
mg/L = milligrams per liter

Glossary

ACGIH	American Conference of Governmental Industrial Hygienists
APHC	U.S. Army Public Health Center
AR	Army regulation
ARDEC	U.S. Army Armament Research, Development and Engineering Center
atm-m3/mol	unit of Henry's Law constant
ATSDR	Agency for Toxic Substances Disease Registry
BAL	bronchoalveolar lavage
BaP	benzo[a]pyrene
BCF	bioconcentration factor
BOD	Biological Oxygen Demand
bp	boiling point
BSI	Brief System Inventory (neurological test)
°C	degrees Celsius
CAS RN	Chemical Abstracts Service Registry Number
CCRIS	Chemical Carcinogenesis Research Information System
CEI	Cumulative Exposure Index
CHO	Chinese hamster ovary
CNS	central nervous system
CPDB	Carcinogenic Potency Database
DA	Department of the Army
DNA	deoxyribonucleic acid
DOD	Department of Defense
DTIC	Defense Technical Information Center
EC_{50}	effective concentration to achieve 50-percent effect
ECHA	European Chemical Agency
ECOSAR	Ecological Structure Activity Relationships
ECOTOX	ECOTOXicology Database System
EPA	U.S. Environmental Protection Agency
EPI	Estimation Programs Interface Suite for Microsoft Windows
ESOH	environment, safety, and occupational health
FDA	U.S. Food and Drug Administration
FSH	Follicle stimulating hormone

GD	gestation day
GHS	Globally Harmonized System
GI	gastrointestinal tract
g/kg	grams per kilogram
g/m^3	grams per cubic meter
g/mol	grams per mol
GRAS	generally recognized as safe
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IC_{50}	Concentration causing 50 percent inhibition
IDLH	immediately dangerous to life or health
IRIS	Integrated Risk Information System (EPA)
IUPAC	International Union of Pure and Applied Chemistry
K_H	Henry's Law constant
K_{OC}	organic carbon-normalized sorption coefficient for soil and sediment
LC_{50}	concentration resulting in 50-percent mortality
LC_{LO}	lowest lethal concentration
LD_{50}	dose resulting in 50 percent mortality
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
log K_{OC}	organic carbon partition coefficient
log K_{OW}	octanol-water partition coefficient
MCL	Maximum Contaminant Level
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
mg/m^3	milligrams per cubic meter
mmHg	millimeters Mercury
MRL	Minimal Risk Level
MW	molecular weight
µg/mL	micrograms per milliliter
µm	micrometer
n/a	not applicable
ND	no data
NIOSH	National Institute for Occupational Safety and Health

nm	nanometer
NO	nitric oxide
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NRC	National Research Council
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
PI	post-instillation
PND	post-natal day
PPE	personal protective equipment
ppm	parts per million
QSAR	Quantitative Structure-Activity Relationship
RDT&E	research, development, test, and evaluation
REL	Recommended Exposure Limit
RfD	reference dose
RNS	reactive nitrogen species
ROS	reactive oxygen species
SCE	sister chromatid exchange
SERDP	Strategic Environmental Research and Development Program
SHE	Syrian hamster embryo
STEL	Short-term Exposure Limit
TLV	Threshold Limit Value
TOXNET	Toxicology Data Network
TWA	time-weighted average
vp	vapor pressure
WHO	World Health Organization