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Toxicology Directorate

Toxicology Assessment for Department of Defense Strategic Environmental Research and Development Program (SERDP) Project WP18-1531: Development of Controlled-Release Corrosion Inhibitors and Healing Agents as Alternatives to Hexavalent Chromium, March 2018–April 2019

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14. ABSTRACT
Corrosion control is a significant problem for military equipment. Many surface treatment materials currently in use on items of military or aerospace materiel contain chromium(VI) as a component, a source of significant human health and environmental hazard. The formulation under evaluation contains no chromium. Most of the proposed components are of low to moderate toxicity and are not a significant concern. Two of the formulation components are associated with some cancer hazard–2-mercaptobenzothiazole and formaldehyde, but both find widespread use in industry and additional investigation is not required for this project.

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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 is 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, testing 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

This report is a toxicological evaluation of a new formulation for a project whose objective is to demonstrate and validate controlled-release corrosion inhibitors as alternatives to the hexavalent chromium [Cr(VI)] (chromate)-containing primers currently used on a variety of weapon systems. The overall project also intends to address accelerated aging protocols that can simulate more accurately, in the laboratory, degradation mechanisms that occur during actual service conditions and that can shorten decision times. This project addresses the DOD goal to reduce the use of Cr(VI) at DOD maintenance depots by 90% or more by the end of Fiscal Year 2020 and to comply with a memorandum calling for the reduction of Cr(VI)-containing primers across the DOD. Alternatives to Cr(VI) primers are important to reduce both hazardous waste and detrimental effects on readiness and the environment, as well as to ensure the safety of workers applying or removing the primers.

1.3 Conclusions

A cancer hazard is associated with 2-mercaptobenzothiazole (2-MBT) and formaldehyde. While there are data gaps for some of the other compounds in this formulation, most of the hazard is derived from typical occupational concerns, such as dermal and ocular irritation, that are normally addressed via personal protective equipment (PPE). For some compounds, there are additional issues, but there are factors in mitigation. For example, while 2-MBT is classified as highly toxic, it is widely used in industrial rubber products. Although there is no epidemiological evidence of serious, 2-MBT-related health issues in humans, workers exposed to 2-MBT have been found to be at increased risk of bladder cancer. Formaldehyde represents a potential concern, as it is a likely human carcinogen. It also poses a hazard for inhalation, oral, and

dermal exposures in addition to moderate dermal, ocular, and neurological effects. The remaining compounds in the alternative formulation are of low to moderate toxicity and not thought to be a serious exposure concern.

1.4 Recommendations

Measures should be taken to address some of the data gaps outlined in this report via experimental work, although none of these factors appears critical to acceptance of this formulation. Notably, there is a question regarding the acute oral toxicity of 2-MBT in rats, with the value of 100 mg/kg being reported but unverified. Little publicly documented experimental information is available for pentaerythrytol tetrakis(3-mercaptopropionate) (PTT). This shortfall could be addressed as time and resources permit but is not critical to the current project. There are no significant information shortfalls for the remaining compounds in the formulation.

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. W74RDV80244410. This Toxicology Assessment addresses, in part, the environment, safety and occupational health (ESOH) requirements outlined in the following—

- Department of Defense Instruction 4715.1E, Environment, Safety, and Occupational Health (ESOH), 2005; Change 1, 2018;
- Army Regulation (AR) 200–1, Environmental Protection and Enhancement, 2007;
- AR 40–5, Preventive Medicine, 2007;
- AR 70–1, Army Acquisition Policy, 2018; and
- Army Environmental Requirement and Technology Assessment (AERTA) Requirement PP-2-02-06, Toxic Metal Reduction in Surface Finishing of Army Weapons Systems.

The Sponsor is the DOD Strategic Environmental Research and Development Program (SERDP). The Principal Investigator is Dr. Luz Marina Calle, NASA John F. Kennedy Space Center.

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 Problem

Cr(VI) is a component of many surface treatment materials currently used on items of military and aerospace materiel. While Cr(VI) has been demonstrated to provide excellent performance, it is a significant human health and environmental hazard. In 2009, the DOD issued a memorandum calling for reduction in use of Cr(VI) across the Department. This project will develop a coating that not only provides a high level of corrosion protection but also employs encapsulation technology to facilitate correction of defects that develop in coated surfaces.

6 Methods

In order to determine the human health and environmental impact of compounds employed in these alternative formulations, it is necessary to identify each compound correctly and 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
2-Mercaptobenzothiazole	149-30-4
Melamine	108-78-1
Formaldehyde	30525-89-4
Pentaerythritol tetrakis(3-mercaptopropionate)	7575-23-7
Sodium dodecyl sulfate	151-21-3

Chemical Substance	CAS Number
Gum arabic	9000-01-5
Tetrahydrofuran	109-99-9
p-Toluenesulfonic acid	104-15-4

The properties necessary to assess fate and transport in the environment (FTE) 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 (NIH) 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); the National Center for Biotechnology Information's PubChem® database, 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), and the International Agency for Research on Cancer (IARC).

Primary references are identified and retrieved via PubMed® and the ProQuest® Databases. TOXNET provides links to a suite of individual databases including ChemIDPlus® (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 (DART) database, the Comparative Toxicogenomics Database (CTD), the Integrated Risk Information System (IRIS), and the Animal Testing Alternatives (ALTBIB) database, as well as several others, including the archived databases for the Chemical Carcinogenesis Research Information System (CCRIS), the Carcinogenic Potency Database (CPDB), and 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) based on 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 (Occupational Safety and Health Administration (OSHA) 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-d	Mixed evidence for carcinogenicity/mutagenicity (B2, 2); Subchronic LOAEL 5–200 mg/kg-d	Positive corroborative evidence for carcinogenicity/ mutagenicity; LOAEL < 5 mg/kg-d
ECOTOXICITY	Acute LC_{50}/LD_{50} >1 mg/L or 1500 mg/kg; Subchronic EC_{50} >100 µg/L or LOAEL >100 mg/kg-d	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-d	Acute LC_{50}/LD_{50}<100 µg/L or <150 mg/kg; Subchronic LOAEL <10 mg/kg-d

Legend:

LC_{50} = concentration expected to result in 50% lethality to a population of test animals
LOAEL = lowest-observed adverse effect level
mg/kg-d = milligrams per kilogram per day
mg/L = milligrams per liter
µg/L = micrograms per liter
Note:
[1] Modified from Howe et al. 2006

7 Results

7.1 Physical and Chemical Properties

Table 3 summarizes the physical and chemical properties of the alternative 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 vp, K_{OW}, K_{OC}, and K_H are typically negligible.

Table 3. Physical Properties

Compound	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
2-Mercaptobenzothiazole	167.244[a]	180.2–181.7[a]	Dec[a]	51[a]	2.41[a]	2.51–3.55[a]	4.1E-11[a]	<1.9E-06[a]
Melamine	126.12[b]	354[b] (exp)	Sublimes[b]	3240[b] (exp)	-1.37[b] (exp)	5[3] (est)	1.84E-14[2] (est)	3.59E-10 at 20ºC[b]
Formaldehyde	30.026[c]	-92[c]	-19.1[c]	Miscible[c]	0.35[c]	1.567[d]	3.27E-07[d]	3.890[c]
Pentaerythrytol tetrakis(3-mercaptopropionate)	488.64[e]	-40.09[f]	275 at 1 mmHg[f]	5.224[g]	3.03[f]	2.227[g]	3.62E-17[g]	4.8E-11[g]
Sodium dodecyl sulfate	288.378[h]	205.5[h]	Dec	1.5E+05[h]	1.6[h]	3.50[h]	1.8E-07[i]	4.7E-13[h]
Gum arabic	≥240,000[J]	ND	ND	Highly soluble[J]	ND	ND	ND	Negligible[J]
Tetrahydrofuran	72.107[k]	-108.44[k]	65.0[k]	Miscible[l]	0.46[k]	1.31[m]	7.05E-05[k]	132[l]
p-Toluenesulfonic acid	172.019[n]	106[o]	140[o]	Very soluble[o]	0.9[n]	0.582[m]	2.78E-09[p]	2.7E-06[p]

Legend:
ºC = degrees Celsius
Dec = decomposes
g/mol = grams per mol
mmHg = millimeters Mercury
ND = No Data

Key:
a = PubChem 2019a
b = PubChem 2019b
c = PubChem 2019c
d = ATSDR 1999
e = ChemIDPlus 2019

f = Sigma-Aldrich 2014
g = EPI Suite 4.11 prediction
h = PubChem 2019e
i. = HSDB 2000
j = HSDB 2002
k. = PubChem 2019
l. = NIOSH 2018
m. = calculated from mean K_{oc} value
n. = PubChem 2019g
o. = Budavari 1996
p. = HSDB 1995

7.2 Compound Summaries

Table 4 summarizes the mammalian toxicity data. Tables 5 and 6 present assessments of human health and environmental toxicity, respectively, for each formula component. 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	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Genotoxicity	Carcinogenicity
2-Mercaptobenzo-thiazole	100[a]	71.3[b]	7.5E-03[b]	Sensitizer[q]	Irritant[a]	Negative[a]	Possible[a]
Melamine	3296[c]	112.5[d]	1500[b]	Negative[a]	Mild irritant[e]	Negative[f]	Positive in male rats[f]
Formaldehyde	800[g]	ND	1.07[g]	Irritant, likely sensitizer[h]	Irritant[h]	Positive	Probable human carcinogen[g]
Pentaerythrytol tetrakis(3-mercaptopropio-nate)	896.4[b]	722.5[b]	8.5E-05[b]	Unlikely irritant; possible sensitizer[b]	Possible mild irritant[b]	Negative[i]	Negative[i]
Sodium dodecyl sulfate	1288[j]	ND	3.900[j]	Irritant[k]	Irritant[b]	Negative[j]	Negative
Gum arabic	ND	ND	ND	ND	ND	ND	Negative[l]
Tetrahydrofuran	1650[m]	127.8[b]	6.10[n]	Irritant[n]	Severe irritant; corrosive[n]	Negative[n]	Possible carcinogen[n]
p-Toluenesulfonic acid	1410[o]	60.3[e]	>10[e]	Irritant[o]	Serious irritant, corrosive[o]	Negative[o]	Negative[o]

Legend:
ND = No data
Key:
a = PubChem 2019a
b = Toxicity Prediction Komputer Assisted Technology (TOPKAT) (BIOVIA™ 2015) model prediction
c = Trochimowicz et al. 2001
d = Melnick et al. 1984
e = TOPKAT database entry
f = PubChem 2019b
g = PubChem 2019c
h = ATSDR 1999
i = Sigma-Aldrich 2014

j = PubChem 2019e
k = Sigma-Aldrich 2018
l = NTP 1982
m = HSDB 2011
n = PubChem 2019f
o = PubChem 2019g

Table 5. Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
2-Mercaptobenzo-thiazole	High	High	Mod	Mod	Mod	
Melamine	Low	Low	Low	Mod	Unknown	
Formaldehyde	Mod	Mod	Mod	High	High	
Pentaerythrytol tetrakis(3-mercaptopropionate)	Mod	High	Mod	Low	Low	Possible developmental/ reproductive toxicant
Sodium dodecylsulfate	Mod	Low	Mod	Mod	Low	
Gum Arabic	Low	Low	Low	Low	Low	
Tetrahydrofuran	Mod	Low	Mod	Mod	Mod	
p-Toluenesulfonic acid	Mod	Low	Mod	High	Low	Possible developmental/ reproductive toxicant

Table 6. Ecotoxicity Assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
2-Mercaptobenzo-thiazole	Low	Low	Unk	High	Low	
Melamine	Low	ND	ND	Low	ND	
Formaldehyde	Mod	Low	Unk	Mod	Unk	
Pentaerythrytol tetrakis(3-mercaptopropionate)	Low	Mod	Unk	Mod	Unk	
Sodium dodecylsulfate	Mod	Mod	Unk	Mod	Unk	
Gum arabic	Low	Low	Low	Low	Low	
Tetrahydrofuran	Low	Low	Unk	Mod	Unk	
p-Toluenesulfonic acid	Low	Low	Unk	Mod	Unk	

7.3 2-Mercaptobenzothiazole [2-MBT]

7.3.1 General Information

2-MBT (shown in Figure 1), is a pale yellow to tan crystalline powder with a disagreeable odor. Synonyms include 2-benzothiazolethiol, 1,3-benzothiazole-2-thiol, benzothiazolethiol, and captax. The International Union of Pure and Applied Chemistry (IUPAC) name is 3H-1,3-benzothiazole-2-thione. 2-MBT is used as an anti-fungal agent, as a vulcanizing accelerator in rubbers, and to protect copper and copper alloys against corrosion (PubChem 2019, HSDB 2015).

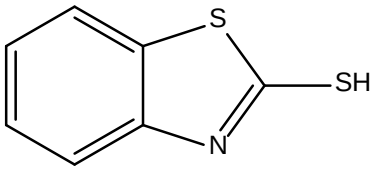

Figure 1. 2-MBT

7.3.2 Toxicology Data

7.3.2.1 Oral

The acute oral LD_{50} is reported to be 100 mg/kg in rats and 1851 mg/kg in mice. This value appears to be inconsistent with other acute toxicity numbers for rats (PubChem 2019a).

TOPKAT modeling predicts an acute oral LD_{50} in rats of 356.9 mg/kg at high confidence, which seems more appropriate although still indicating high oral toxicity.

An experimental LOAEL derived from a National Toxicology Program study (NTP 1988) is reported in the TOPKAT database as 268 mg/kg-day; however, this is inconsistent with the acute LD_{50} reported above.

7.3.2.2 Inhalation

No experimental data were found. TOPKAT predicts an inhalation LC_{50} of 7.5 mg/m^3-hour at low confidence.

7.3.2.3 Dermal

2-MBT is reported to be a skin sensitizer (PubChem 2019a). Contact dermatitis has been reported from exposure to rubber gloves, condoms, and rubber earplugs (HSDB 2015).

7.3.2.4 Ocular

2-MBT is reported to be an ocular irritant (PubChem 2019a).

7.3.2.5 Development and Reproduction

Rodwell et al. (1990) administered 2-MBT by oral gavage to both rats and rabbits. Rats received doses of up to 1800 mg/kg-day in corn oil, and rabbits up to 300 mg/kg-day in 1% methylcellulose. Clinical signs, body weights, and liver weights (rabbits only) were recorded. Maternal effects were produced in rats as evidenced by clinical signs at doses of 1200 and 1800 mg/kg-day and reduced body weight gain and food consumption at 1800 mg/kg-day. In rabbits, maternal effects included slightly reduced body weight gain and increased liver weight at 300 mg/kg-day. In both species, no adverse effects were observed in C-section parameters or in fetal morphological exams. In the rat, a marginal increase in postimplantation loss was considered equivocal at 1800 mg/kg-day; no increase was observed in a 2-MBT range-finding study at dosages up to 2200 mg/kg-day. The NOAEL for developmental toxicity was considered to be 1800 mg/kg-day in the rat and 300 mg/kg-day in the rabbit.

7.3.2.6 Neurotoxicity

Seizures have been reported in animals given 335 mg/kg (HSDB 2015).

7.3.2.7 Genotoxicity

2-MBT was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without metabolic activation. In the presence of rat liver S9 fractions, 2-MBT increased the frequency of chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells, as well as mutations at the TK locus of mouse L5178Y lymphoma cells (PubChem 2019a).

An investigation of a possible genotoxic mechanism for carcinogenicity of 2-MBT was conducted by Brewster et al. (1989) by examining the covalent binding of 2-MBT to deoxyribonucleic acid (DNA) from rat tissues. Male and female Fisher 344 rats were dosed via gavage with 375 mg/kg body weight of radiolabeled 2-MBT. Eight hours after dosing, the liver, adrenal gland, pancreas, pituitary gland, and femur were harvested from each animal. Assay results from liver demonstrated only 0.6% of the 2-MBT radioactivity, while the other tissues exhibited less than 0.03% of the administered dose. These results suggest 2-MBT does not significantly bind to DNA.

7.3.2.8 Carcinogenicity

2-MBT is considered to be a possible human carcinogen (PubChem 2019a).

Epidemiological studies by Whittaker et al. (2004) indicate workers exposed to 2-MBT have an increased risk of bladder cancer. Review of the epidemiological and toxicological dataset for 2-MBT indicated induction of renal pelvis transitional cell tumors is the most sensitive and relevant

health effects endpoint. A Total Allowable Concentration (TAC) in drinking water of 600 µg/L was derived for 2-MBT.

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

If released to soil, 2-MBT is expected to have low to moderate mobility based upon a measured K_{oc} range of 326–3560 (log K_{oc} 2.51–3.55). The pKa of 2-MBT is 7.03, indicating that this compound will exist partially in the anion form in the environment. Compared to their neutral counterparts, anions generally do not adsorb more strongly to soils containing organic carbon and clay. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 4.1 $x10^{-11}$ atm-m^3/mol. Based upon its vapor pressure, 2-MBT is not expected to volatilize from dry soil surfaces (PubChem 2019a).

If released to air, a vapor pressure of 2.25 x 10^{-8} mm Hg at 20ºC indicates 2-MBT will exist in both the vapor and particulate phases in the atmosphere. Vapor-phase 2-MBT will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 9.5 hours. Particulate-phase 2-MBT will be removed from the atmosphere by wet and dry deposition. 2-MBT absorbs at wavelengths >290 nm and, therefore, may be susceptible to direct photolysis by sunlight (PubChem 2019a).

A bioconcentration factor (BCF) of <8 for 2-MBT was measured in fish, using carp (*Cyprinus carpio*) which were exposed over a 6-week period. This BCF suggests the potential for bioconcentration in aquatic organisms is low (PubChem 2019a).

7.3.2.9.2 Ecotoxicity

2-MBT is reported to be very toxic to aquatic life with long-term effects (PubChem 2019a).

The 48-hour LC_{50} in water flea (*Ceriodaphnia dubia*) is reported to be 4.190 mg/L, and the 96-hour LC_{50} for bluegill (*Lepomis macrochirus*) is 1.900 mg/L. The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) is 0.420 mg/L, and the 96-hour LC_{50} for channel catfish (*Ictalurus punctatus*) is 1.650 mg/L (PubChem 2019a).

When administered to birds as a gavage bolus, 2-MBT is almost non-toxic; it is only slightly toxic to birds when added to their food and consumed in a less concentrated form. 2-MBT is considered highly toxic to freshwater fish and moderately toxic to freshwater invertebrates (HSDB 2015).

2-MBT is toxic to activated sludges, impacting degradation. A bacteriostatic effect was observed towards *E. coli*, *Sarcina lutea*, *Staphylococcus aureus*, and a 2-hydroxybenzothiazole-degrading isolate. 2-MBT caused membrane disturbances as measured by induced potassium effluxes from the cell. It appears 2-MBT interferes with an oxidoreduction step in membrane-bound systems and probably also interferes with metabolic reactions not related to the respiratory chain (DeWever et al. 1997).

7.3.2.9.3 Degradation/Treatment

Results of biodegradation screening tests indicate that 2-MBT is resistant to environmental biodegradation and not readily biodegradable in soil or water. Photodegradation can occur on soil surfaces exposed to sunlight (PubChem 2019a).

7.4 Melamine

7.4.1 General Information

Melamine (shown in Figure 2) exists as colorless to white monoclinic crystals, prisms, or as a white powder. The IUPAC name is 1,3,5-triazine-2,4,6-triamine (PubChem 2019b). Melamine's primary industrial use is in the preparation of melamine resins used in preparation of melamine-formaldehyde synthetics for items such as laminates, glues, molding compounds, flame retardants and super-plasticizers for concrete, among other applications (Organization for Economic Cooperation and Development (OECD) 1999). Melamine is sometimes illegally added to food products in order to increase the apparent protein content, but new instrumental methods of analysis have greatly reduced this occurrence (PubChem 2019b). Melamine was added to pet food in 2007, resulting in several deaths. Infant formula was also found to be contaminated with melamine and the related compound, cyanuric acid. Only traces of melamine and cyanuric acid were found in infant formula sold in the U.S., but in China, 50,000 infants were hospitalized after consuming adulterated infant formula, and at least 4 died. It has also been demonstrated that melamine present in feed for milk cows will appear in the milk within 8 hours of administration (Cruywagen et al. 2009).

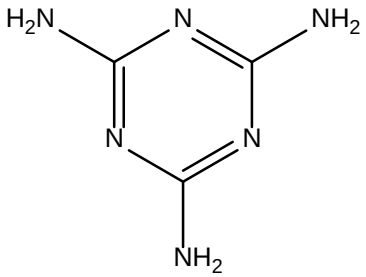

Figure 2. Melamine

7.4.2 Toxicology Data

7.4.2.1 Oral

Observed toxic effects of melamine alone in animals in controlled studies occur only after high-dose exposures. All information to date indicates melamine is metabolically inert. Kidney problems associated with melamine ingestion appear to result from formation of crystals in the kidney, usually in conjunction with melamine-related compounds, such as cyanuric acid, that are commonly present as contaminants in melamine formulations. This crystal formation has been

shown to take place at various dose levels and is a threshold- and concentration-dependent phenomenon.

The acute oral LD_{50} in rats is 3160 mg/kg for males and 3850 mg/kg for females (Trochimowicz et al. 2001).

The acute oral LD_{50} in mice is 4550 mg/kg. Signs of toxicity following lethal doses include lacrymation, dyspnea, intermittent tremors, and coma preceding death. Vasodilation in tail and ears, and paralysis of forequarters were also observed (Trochimowicz et al. 2001).

In dogs given a single oral dose of 2400 mg/kg, melamine produced diuresis and crystalluria. Dimelamine monophosphate was found as a urinary product (Trochimowicz et al. 2001).

Pet food adulterated with melamine has resulted in renal failure in dogs and cats. Affected animals exhibit uremia, anorexia, vomiting, lethargy, polyuria, azotemia, and hyperphosphatemia. Distal tubular lesions were present in affected animals, and unique polarizable crystals with striations were present in distal tubules or collecting ducts; proximal tubules were largely unaffected. The concentrations of melamine that produce these effects are not known (Brown et al. 2007).

Melamine was administered orally in feed to male Fisher 344 rats at doses equivalent to 63-1267 mg/kg for 4 weeks. The study was conducted to evaluate urolithiasis (formation of urinary calculi) induction by melamine. In-life observation indicated a significant dose-related depression in body weight gain, elevated water intake, and altered food consumption pattern. Melamine produced a dose-dependent incidence of urinary calculi and urinary bladder hyperplasia. With one exception, all animals (40 per group) with hyperplasia had calculi. The NOAEL was determined to be equivalent to 63 mg/kg-day (OECD 1999).

Melamine produced strong diuretic effects in rat and dogs fed 126 mg/kg daily for 1 to 4 weeks. No histopathological effects were seen (Trochimowicz et al. 2001).

Melamine was administered in the diet to F344 rats or B6C3F1 mice for 13 weeks. The dose levels ranged from 750–18,000 ppm (mg/kg) for rats and 6000–18,000 ppm (mg/kg) for mice. Compound-related lesions were observed in the urinary tract. Most noticeable was the development of uroliths (urinary bladder stones), which occurred at a greater frequency in males than females of either species. Increased incidence of urinary bladder stones and hyperplasia of the bladder epithelium were observed in male rats (Melnick et al. 1984).

Chronic feeding studies were carried out over a 2-year period at a dietary level of 1000 ppm without ill effect. Dogs received melamine at 30,000 ppm in their feed for a period of 1 year. After 60–90 days, the dogs showed melamine crystalluria, which persisted throughout the remainder of the 1-year observation. At autopsy, gross and microscopic examination of tissues revealed no abnormality attributable to the feeding of melamine (Trochimowicz et al. 2001).

Melamine was administered in feed to F344 rats or B6C3F1 mice for 103 weeks. Dose levels were 2250 or 4500 ppm for male rats and mice of both sexes; female rats received 4500 or 9000 ppm. Compound-related lesions were observed in the urinary tract. Most noticeable was

the development of uroliths, which occurred at a greater frequency in males than in females of either species. Transitional cell carcinomas in the urinary bladder of male rats occurred at a significantly higher incidence ($p \leq 0.016$) in the 4500 ppm group (8/49) than in the controls (0/45). Seven of the eight male rats with transitional-cell carcinomas of the urinary bladder also had bladder stones. There was a statistically-significant association ($p \leq 0.001$) between bladder stones and bladder tumors in male rats fed melamine at the high dose. Urinary bladder tumors were not observed in the low-dose male rat group; bladder stones were observed in one rat. Chronic inflammation of the kidney was observed in female rats at both dose levels (Melnick et al. 1984, NTP 1983).

7.4.2.2 Inhalation

No experimental data were found. TOPKAT modeling predicts an acute inhalation LC_{50} of 1500 g/m^3-hour at high confidence, indicating lack of direct toxicity. Thermal decomposition results in production of toxic nitrogen oxides and hydrogen cyanide (HSDB 2012).

7.4.2.3 Dermal

Human subjects given patch tests with melamine showed no evidence of irritation or sensitization (PubChem 2019b).

The dermal LD_{50} for rabbits is greater than 1000 mg/kg, indicating no dermal toxicity (HSDB 2012).

Application of melamine to rabbit skin caused no primary skin irritation or signs of systemic toxicity when applied under an impervious cover at doses as high as 1 g/kg for 18 hours (Trochimowicz et al. 2001).

Melamine applied under a rubber cuff to guinea pig skin as a 1% solution in water produced little to no irritation (Trochimowicz et al. 2001).

7.4.2.4 Ocular

An entry in the TOPKAT database indicates melamine is a mild ocular irritant.

7.4.2.5 Development and Reproduction

Female Wistar rats received melamine orally in feed at doses of 1500, 4500, and 15,000 ppm. Administration of melamine during organogenesis showed signs of maternal toxicity only at 15,000 ppm, along with reduced food consumption, body weight loss, reduced body weight gain, and corrected body weight gain. Maternal symptoms included hematuria (23/25 animals), indrawn flanks (7/25 animals) and piloerection (1/25 animals), but maternal symptoms were reversed upon stopping treatment. Melamine appeared to have no influence on gestational parameters, and showed no signs of developmental toxicity. There were no signs of teratogenicity at doses up to and including 15,000 ppm (European Chemicals Board (ECB) 2007).

7.4.2.6 Neurotoxicity

An and Sun (2017) recently published a review addressing neurotoxicity of melamine. Melamine appears to represent a neurological hazard only during development. Animal studies indicate melamine can transit the blood-brain barrier and the placenta. Experimental observations have included an increase in reactive oxygen species, apoptosis, hyperpolarization, spontaneous neuronal firing, and disrupted metabolism. Melamine can also apparently affect the central nervous system (CNS) and has induced deficits in learning and memory in adolescent rats.

7.4.2.7 Genotoxicity

Melamine tested negative in Ames *Salmonella typhimurium* strains TA100, TA98, TA97, and TA102, with or without microsomal (S9) activation, at concentrations up to 5000 µg/plate (ECB 2007). Melamine was also negative in strains TA1535 and TA1537, with or without microsomal activation (IARC 1986).

Increased numbers of micronuclei were not observed in CD-1 mice receiving melamine at 1000 mg/kg-day either 30 or 48 hours after dosing, or after receiving 2 doses 24 hours apart and sacrificed after 48 or 72 hours (ECB 2007).

Melamine tested negative in Chinese hamster ovary (CHO) cells with or without microsomal activation at concentrations of 0, 240, 270, or 300 µg/mL (ECB 2007).

Melamine was negative in the HGPRT forward mutation assay in CHO cells at concentrations from 600 to 1000 µg/mL (ECB 2007).

Melamine also tested negative in the L5178Y tk+/- mouse lymphoma forward mutation assay. Cultures were exposed for 4 hours then cultured for 2 days before plating on soft agar, with or without trifluorothymidine, 3 µg/mL (McGregor et al. 1988).

Sex-linked recessive dominant lethal mutations were not induced in *Drosophila melanogaster* given melamine in the diet (IARC 1986).

7.4.2.8 Carcinogenicity

Melamine is not classifiable as to its carcinogenicity in humans (PubChem 2019b).

In animals, melamine produces urinary bladder tumors via a non-DNA-reactive mechanism under conditions when bladder calculi were produced in male rats. The effective daily dose to induce tumors in 50% of the test animals (TD_{50}) has been calculated to be 735 mg/kg-day. Only male rats have been demonstrated to produce tumors; no tumors were found in female rats or in mice of either gender (CPDB 2007, HSDB 2009).

7.4.2.9 Ecotoxicology

7.4.2.9.1 Fate and Transport

If released to soil, melamine is expected to have very high mobility based upon an estimated K_{oc} of 5. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of 1.8×10^{-14} atm-m^3/mol. If released into water, melamine is not expected to adsorb to suspended solids and sediment based upon the estimated K_{oc}. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated K_H. An estimated BCF of 3 suggests bioconcentration in aquatic organisms is low. If released to air, a vapor pressure of 3.59×10^{-10} mmHg at 20ºC indicates melamine will exist solely in the particulate phase in the atmosphere. Particulate-phase melamine will be removed from the atmosphere by wet or dry deposition (PubChem 2019b).

7.4.2.9.2 Ecotoxicity

Melamine-cyanuric acid crystals have been shown to develop in mice, pig, cat, and fish kidneys, when test animals are dosed with both melamine and its analogue cyanuric acid. The crystals that form in pigs and fish are identical to those seen in cats (U.S. Food and Drug Administration (FDA) 2018).

The EPA's ECOSAR program models melamine as both a melamine and an amino-meta aniline. The minimum 96-hour LC_{50} in green algae is 2.78 mg/L, the minimum 48-hour LC_{50} in *Daphnia* is 6.23 mg/L, and the minimum 96-hour LC_{50} in fish is 391 mg/L.

Exposure of the bloodfluke *Biomphalaria glabrata* for 45 days to sublethal concentrations (500, 1000 and 2000 mg/L) of melamine in water caused a concentration-dependent decrease in reproductive ability (Ramusino & Tenconi 1980).

Melamine at 500 and 1000 mg/L lowered the rate of Rainbow trout (*Salmo gairdneri*) egg hatchability and produced increased incidence of exposed larvae at 125 and 250 mg/L (Ramusino & Vailati 1982).

Fish and pigs were fed targeted doses of melamine (400 mg/kg), cyanuric acid (400 mg/kg) or melamine and cyanuric acid (400 mg/kg of each compound) for 3 days and euthanized 1, 3, 6, 10 or 14 days after administration ceased. Fresh, frozen, and formalin-fixed kidneys were examined for crystals. Edible tissues were collected for residue analysis. All animals fed the combination of melamine and cyanuric acid developed gold-brown renal crystals of radial sphere pattern similar to those detected in cats. Melamine and cyanuric acid residues were identified in edible tissues of fish (Reimschuessel et al. 2008).

Between November 2003 and September 2006, 300 to 400 45-to-60-day-old, farm-kept Iberian piglets developed anorexia, polydipsia, and lethargy. Piglets were from five different farms in western Spain. Morbidity was between 40% and 60%, and mortality ranged from 20–40 percent of the total population of post-weaning piglets. Postmortem examinations of nine animals found their kidneys to be enlarged with yellow foci in the cortex and medulla. Microscopically, crystals were observed within the lumina of dilated distal tubules and collecting ducts, causing flattening of the renal tubular epithelial cells. Toxicologic analysis of fixed kidney tissues from four piglets

found the presence of melamine and related compounds. Melamine concentrations were determined to be 9200–29,000 mg/kg (Gonzalez et al. 2009).

7.4.2.9.3 Degradation/Treatment

No biodegradation of melamine using a standard 5-day Biological Oxygen Demand (BOD) test was observed, suggesting that biodegradation may not be an important environmental fate process. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions (PubChem 2019b).

7.5 Formaldehyde

7.5.1 General Information

Formaldehyde (shown in Figure 3) is a colorless poisonous gas with a wide range of uses, including the manufacture of resins and textiles, as a disinfectant, and as a laboratory fixative or preservative. Synonyms include formalin (10% solution), methanal, formol, formic anhydride, oxomethane, and others. Formaldehyde is a Standardized Chemical Allergen that functions via increased histamine release and cell-mediated immunity. Formaldehyde is readily soluble in water; a 10% solution is typically used as a disinfectant and to preserve biological specimens. Environmentally, formaldehyde is found in the atmosphere, smoke from fires, automobile exhaust, and cigarette smoke. Small amounts are produced during normal metabolic processes in most organisms, including humans (PubChem 2019c).

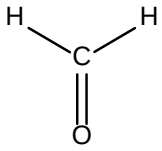

Figure 3. Formaldehyde

7.5.2 Toxicology Data

Effects of formaldehyde have been discussed extensively in ATSDR's *Toxicological Profile of Formaldehyde* (ATSDR 1999) and a subsequent *Addendum* (ATSDR 2010).

7.5.2.1 Oral

The acute oral LD_{50} in rats is reported to be 800 mg/kg; the corresponding value in the mouse is 42 mg/kg (PubChem 2019c).

Formaldehyde poses an acute oral toxicity hazard. The lowest lethal dose for humans taking formaldehyde orally is 36 mg/kg (PubChem 2019c). The ATSDR noted there were no effects in animals receiving less than 49 mg/kg-day (ATSDR 2010).

7.5.2.2 Inhalation

Controlled-exposure human studies have found that short-term inhalation exposures to concentrations ranging from 0.4 to 3 ppm can produce symptoms of mild to moderate irritation of the eyes, nose, and throat (ATSDR 2010).

The acute inhalation LC_{50} in rats for a 4-hour exposure is reported to be 1070 mg/m^3 (PubChem 2019c).

Formaldehyde is harmful if inhaled and may cause allergy or asthma symptoms or breathing difficulties if inhaled. Evidence of sensitization has been reported. Inhalation of high concentrations may cause lung edema but only after initial corrosive effects have become apparent on the eyes and the upper respiratory tract (PubChem 2019c).

7.5.2.3 Dermal

Formaldehyde causes dermal irritation and is likely a dermal sensitizer (PubChem 2019). A fraction (usually < 5%) of individuals exposed via patch testing or similar challenge typically are positive (ATSDR 1999).

7.5.2.4 Ocular

Formaldehyde causes serious eye damage (PubChem 2019c). Exposure to formaldehyde in the atmosphere at concentrations in the range 0.4–3.0 ppm and above can cause eye irritation (ATSDR 1999).

7.5.2.5 Development and Reproduction

Developmental effects have not been observed in animal studies with formaldehyde (PubChem 2019c).

Reports of higher rates of spontaneous abortion in female occupational workers have been characterized as inconsistent, and effects on pregnancy and fetal development in animals were not seen below maternally toxic concentrations (ATSDR 2010).

7.5.2.6 Neurotoxicity

Experiments in humans by Bach and colleagues have demonstrated decreased performance in tests designed to access distractibility, short-term memory, and the capability to understand and perform certain tasks. Decreased performance was correlated with increasing exposure to formaldehyde (ATSDR 2010).

7.5.2.7 Genotoxicity

Formaldehyde has been demonstrated to cause aneuploidy and structural chromosome alterations in cultured myeloid progenitor cells. The level of chromosome alterations followed a pattern frequently observed in acute myeloid leukemia and may indicate a potential mechanism underlying formaldehyde-induced leukemogenesis (Lan et al. 2015).

Obe and Beek (1979) found formaldehyde induced a 1.5- to 3-fold increase in Sister Chromatid Exchange in human lymphocytes in culture.

A majority of genotoxicity tests show that formaldehyde can induce genotoxic effects in various organisms and cell types. Environment Canada/Health Canada and the WHO have concluded formaldehyde is a weak genotoxic (ATSDR 2010b).

7.5.2.8 Carcinogenicity

Formaldehyde is a classified by the ATSDR, EPA, and American Conference of Governmental Industrial Hygienists® (ACGIH®) as a probable human carcinogen based on limited evidence in humans and sufficient evidence in animals. The IARC considers there to be sufficient evidence in humans (PubChem 2019c).

In its 2006 monograph, the IARC concluded that the overall evidence in humans does not support a causal role for formaldehyde in cancers of the respiratory tract. However, the IARC does believe there is sufficient causal evidence for association of formaldehyde with leukemia (ATSDR 2010b).

7.5.2.9 Ecotoxicology

7.5.2.9.1 Fate and Transport

The fate of formaldehyde in soil is not fully understood, but the compound is biodegradable to carbon dioxide and water or formic acid under both aerobic and anaerobic conditions. Formaldehyde is also biologically active, reacting readily with phenol, amine, amide, sulfide, purine, and pyrimidine functional groups. Formaldehyde is also subject to spontaneous polymerization (ATSDR 2010b).

In air, formaldehyde reacts with NO_3 radicals with a lifetime of 83 days (Atkinson & Arey 2003).

7.5.2.9.2 Ecotoxicity

There is an extensive amount of formaldehyde toxicity information in the EPA ECOTOX database (EPA 2019). Four-day EC_{50} levels for green algae are in the range of 0.7–3.3 mg/L, 48-hour EC_{50} levels in *Daphnia* range from 6 to 30 mg/L, and the 96-hour LC_{50} in the standard fish test species (fathead minnow, *Pimephalas promelas*, and rainbow trout, *Oncorhynchus mykiss*) ranges from 2 to 550 mg/L. These values generally place formaldehyde in the moderately toxic category, comparable to GHS Categories I and II.

7.5.2.9.3 Degradation/Treatment

Uncatalyzed decomposition is very slow below 300ºC; extrapolation of kinetic data to 400ºC indicates rate of decomposition is about 0.44 percent/min at 1 atm (PubChem 2019c).

7.6 Pentaerythrytol tetrakis(3-mercaptopropionate) [PTT]

7.6.1 General Information

PTT (shown in Figure 4) is a clear, colorless viscous liquid with a sulfur stench (Sigma-Aldrich 2014). The IUPAC name for PTT is [3-(3-sulfanylpropanoyloxy)-2,2-bis(3-sulfanylpropanoyl-oxymethyl)propyl] 3-sulfanylpropanoate (PubChem 2019d). Other systematic names for this compound are 3-mercapto-1,1'-(2,2-bis((3-mercapto-1-oxopropoxy)methyl-1,3-propanediyl) propanoic acid ester and 3-mercapto-2,2-bis((3-mercapto-1-oxopropoxy)methyl)-1,3-propandiyl propanoic acid ester (ChemIDPlus 2019).

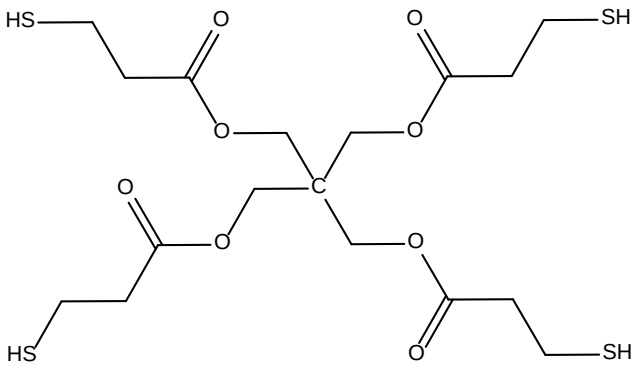

Figure 4. PTT

7.6.2 Toxicology Data

7.6.2.1 Oral

A supplier safety data sheet categorizes PTT in GHS Category 4; the acute oral LD_{50} in female rats is reported to be 1000–2000 mg/kg (Sigma-Aldrich 2014). Overall, PTT is assessed to be moderately toxic.

TOPKAT modeling predicts an acute oral LD_{50} in rats of 896.4 mg/kg at low confidence. The chronic LOAEL is predicted to be 722.5 mg/kg-day at high confidence.

7.6.2.2 Inhalation

No experimental data are available. TOPKAT modeling predicts an acute inhalation LC_{50} in rats of 85.8 µg/m^3-hour (an unreasonably low number) at low confidence. This is an extreme level of toxicity not typically associated with chemical compounds and not likely to be accurate. It is also unlikely to be of importance since the probability of inhalation exposure is low.

7.6.2.3 Dermal

PTT is reported to possibly be a skin sensitizer (PubChem 2019d). A supplier safety data sheet categorizes PTT in GHS Category 1 (Sigma-Aldrich 2014).

TOPKAT modeling predicts PTT is an unlikely irritant but a possible severe sensitizer.

7.6.2.4 Ocular

No eye irritation was reported in an experimental evaluation in the rabbit, conducted in accordance with OECD Guideline 405 (Sigma-Aldrich 2014).

TOPKAT modeling predicts PTT will possibly be a mild irritant.

7.6.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts PTT will be a developmental or reproductive toxicant at low confidence.

7.6.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.6.2.7 Genotoxicity

Tests in mammalian and bacterial cell cultures were reportedly negative (Sigma-Aldrich 2014).

7.6.2.8 Carcinogenicity

PTT is not listed as carcinogenic by the IARC, ACGIH, NTP, or OSHA (Sigma-Aldrich 2014).

7.6.2.9 Ecotoxicology

7.6.2.9.1 Fate and Transport

If released to soil, PTT is expected to have a low mobility in groundwater due to limited solubility, and it is unlikely to pose a hazard to surface or drinking water. Partition from water or wet surfaces is expected to be insignificant due to a calculated K_H of 3.62×10^{-17} atm-m^3/mol. Vaporization from dry surfaces is also expected to be insignificant due to vapor pressure, so any

PTT present in the atmosphere will be present in particulate form. Tendency to bioaccumulate is expected to be low.

7.6.2.9.2 Ecotoxicity

PTT is classified as “very toxic to aquatic life with long lasting effects” by the GHS (PubChem 2019d). A supplier safety data sheet categorizes PTT in GHS Category I for acute aquatic toxicity and chronic aquatic toxicity (Sigma-Aldrich 2014).

The EC_{50} for a 72-hour test in the green algae *Desmodesmus subspicatus* was greater than 0.12 mg/L. The 96-hour LC_{50} in rainbow trout (*Oncorhynchus mykiss*) was 0.42 mg/L (Sigma-Aldrich 2014).

The EPA’s ECOSAR program models PTT in the thiol/mercaptan class. The 96-hour EC_{50} in green algae is predicted to be 0.919 mg/L, the 48-hour LC_{50} in *Daphnia* is predicted to be 1.26 mg/L, and the 96-hour LC_{50} in fish is predicted to be 7.07 mg/L. The prediction for green algae drives the GHS classification for acute toxicity to Category I.

7.6.2.9.3 Degradation/Treatment

PTT is not predicted to be biodegradable according to the EPA’s Estimation Programs Interface (EPI) Suite 2.0 models (EPA 2018); environmental persistence is projected to be weeks to months.

According to the EPA’s EPI Suite models, PTT will be poorly removed (< 3.5%) by physical processes at wastewater treatment plants.

7.7 Sodium dodecyl sulfate [SDS]

7.7.1 General Information

SDS, also known as sodium lauryl sulfate, is an anionic surfactant. It is a white to pale yellow solid with a mild odor. Its alternative CAS numbers are 1335-72-4 and 8012-56-4 (PubChem 2019e). Figure 5 illustrates the molecular structure of SDS.

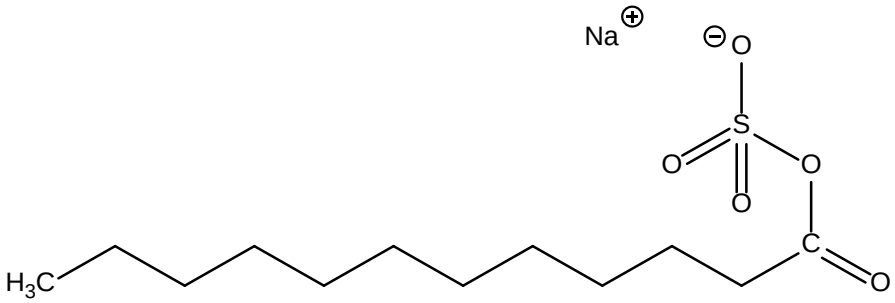

Figure 5. SDS

7.7.2 Toxicology Data

7.7.2.1 Oral

The acute oral LD_{50} in rats is reported to be 1288 mg/kg, corresponding to GHS Category 4. Ingestion of large amounts causes irritation of the stomach (PubChem 2019e).

7.7.2.2 Inhalation

The acute inhalation LC_{50} in rats is reported to be 3900 mg/m^3-hour, corresponding the GHS inhalation Category 4. Inhalation of dust causes sneezing and coughing (PubChem 2019e).

7.7.2.3 Dermal

The LD_{Lo} for dermal toxicity in the rabbit is 10,000 mg/kg. Effects from overexposure include ataxia, changes is structure or function of salivary glands, gastric hypermobility, and diarrhea. Contact with skin causes some irritation (PubChem 2019e).

According to a supplier safety data sheet, SDS is a GHS Category 2 skin irritant (Sigma-Aldrich 2018).

7.7.2.4 Ocular

Dust irritates the eyes and may cause burns on prolonged contact (PubChem 2019e). According to a supplier safety data sheet, SDS is classified as a GHS Category 1 eye irritant (Sigma-Aldrich 2018).

7.7.2.5 Development and Reproduction

No data were found. SDS is not expected to be a developmental or reproductive toxicant.

7.7.2.6 Neurotoxicity

No data were found.

7.7.2.7 Genotoxicity

SDS tests negative in the Ames test for mutagenicity with and without microsomal activation in all five standard test strains of *S. typhimurium*. SDS also tests negative in the micronucleus assay, the sister chromatid exchange assay in Chinese hamster ovary cells, and the mouse lymphoma cell forward mutation assay with and without activation (PubChem 2019d).

7.7.2.8 Carcinogenicity

SDS is not expected to be carcinogenic.

7.7.2.9 Ecotoxicology

7.7.2.9.1 Fate and Transport

If released to soil, SDS is expected to have slight mobility based upon an estimated K_{oc} of 3200. Volatilization from moist soil surfaces or water is not expected to be an important fate process based upon a water solubility of 1.00 $x10^5$ mg/L and because it is a salt. Based upon its estimate vapor pressure, SDS is not expected to volatilize from dry soil surfaces (HSDB 2000).

If SDS is released to air, an estimated vapor pressure of 4.7 x 10^{-13} mm Hg at 25 ºC indicates the compound will exist solely in the particulate phase in the ambient atmosphere. Particulate-phase SDS will be removed from the atmosphere by wet and dry deposition. SDS does not contain chromophores that absorb at wavelengths >290 nm and, therefore, is not expected to be susceptible to direct photolysis by sunlight (HSDB 2000).

An estimated BCF of 71 suggests the potential for SDS bioconcentration in aquatic organisms is moderate (HSDB 2000).

7.7.2.9.2 Ecotoxicity

The 48-hour EC_{50} in *Daphnia* is reported to be 1.8 to 51.5 mg/L. The 96-hour LC_{50} for eastern mosquitofish (*Gambusia holbrooki*) is reported to be 15.1 mg/L (PubChem 2019e).

According to a supplier safety data sheet, SDS is classified in GHS Category II for acute aquatic toxicity and Category III for chronic aquatic toxicity (Sigma-Aldrich 2018).

7.7.2.9.3 Degradation/Treatment

Abiotic degradation is not expected to be an important environmental fate process for SDS due to lack of hydrolysable functional groups (PubChem 2019e).

SDS is 95% biodegradable within 28 days under aerobic conditions (Sigma-Aldrich 2018).

7.8 Gum arabic [Acacia]

7.8.1 General Information

Gum arabic, also known as acacia, is a white to yellow-brown powder. Chemically, gum arabic is a polysaccharide composed primarily of arabinose, rhamnose, galactose, and glucuronic acid with calcium, magnesium, and potassium ions. Its primary use is as a food additive, and it is generally recognized as safe (GRAS). It is also used for relief of inflammation and as a suspending or dispersing agent. Obtained from trees of the genus *Acacia*, gum arabic is the result of an infection, either bacterial or fungal. It is exuded only by unhealthy trees; heat, poor nutrition, and drought stimulate its production (HSDB 2002)

7.8.2 Toxicology Data

Workers exposed to gum arabic have been found to suffer from an allergic condition known as "printer's asthma," characterized by difficulty breathing. Frequency of allergic symptoms depends primarily on the atmospheric gum arabic concentration. Since gum arabic is no longer generally used in printing, having been supplanted by chalk, the incidence of this allergic condition is significantly reduced (HSDB 2002).

7.8.2.1 Oral

Ingested orally, acacia is non-toxic; it is recognized as a GRAS food additive (HSDB 2002).

7.8.2.2 Inhalation

Although gum arabic is non-toxic by inhalation, sensitivity can develop over time (HSDB 2002).

7.8.2.3 Dermal

No data were found.

7.8.2.4 Ocular

No data were found.

7.8.2.5 Development and Reproduction

No data were found.

7.8.2.6 Neurotoxicity

No data were found.

7.8.2.7 Genotoxicity

No data were found.

7.8.2.7 Carcinogenicity

A 2-year study by the NTP found that gum arabic was not carcinogenic in rats or mice (NTP 1982).

7.8.2.8 Ecotoxicology

7.8.2.8.1 Fate and Transport

Although highly soluble in water, gum arabic is a high-molecular-weight polymer and thus not expected to be highly mobile in the environment.

7.8.2.8.2 Ecotoxicity

Gum arabic is not anticipated to cause ecotoxicity.

7.8.2.8.3 Degradation/Treatment

As a naturally-produced polysaccharide, gum arabic is expected to be biodegradable.

7.9 Tetrahydrofuran [THF]

7.9.1 General Information

THF, also known by its IUPAC name, oxolane, is a clear, colorless liquid with an ethereal odor. It is used as a solvent in many applications, including various polymers, and in the preparation of inks, lacquers, and coatings, especially for vinyl polymers (PubChem 2019f). Figure 6 illustrates the molecular structure of THF.

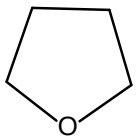

Figure 6. THF

7.9.2 Toxicology Data

7.9.2.1 Oral

The acute oral LD_{50} is reported to be 1650 mg/kg in rats, 2300 mg/kg in mice, and 2300 mg/kg in the guinea pig. The probable oral lethal dose in humans is 50–500 mg/kg (HSDB 2011).

TOPKAT modeling predicts a chronic LOAEL of 127.8 mg/kg at high confidence.

7.9.2.2 Inhalation

The acute inhalation LC_{50} in the rat is reported to be 18,000 to 22,000 ppm for a 4-hour exposure, and 1200 ppm in rabbits for a 4-hour exposure. THF may cause respiratory irritation. Its vapors cause nausea, dizziness, headache, and loss of conciousness (PubChem 2019f). The margin of safety between anesthesia and death is small (HSDB 2011).

Conversion factor: 1 ppm = 2.95 mg/m^3 (NIOSH 2018).

7.9.2.3 Dermal

THF is well absorbed through the skin of rabbits and rats. Dermal exposure results in dry skin,

redness, and pain. THF was rapidly lethal to rats when 10 percent of their body surface was exposed to the liquid solvent (PubChem 2019f).

7.9.2.4 Ocular

THF causes serious eye irritation and damage (PubChem 2019f).

7.9.2.5 Development and Reproduction

Mast et al. (1992) exposed rats and mice to THF at doses up to 5000 ppm by inhalation for 6 hours/day, 7 days a week from Gestation Day (GD) 6–19 for rats and GD 6–17 for mice. Body weights of dams in the 5000-ppm dose group were reduced at euthanization. There were no effects on the percentage of live rat fetuses/litter or on the fetal sex ratio. Fetal body weight was significantly reduced for the 5000-ppm group, but the incidence of abnormalities was not increased. The mean body and uterine weights of mice were reduced for the 1800- and 5000-ppm groups at euthanization, but adjusted maternal weight gain was not affected at 1800 ppm. There was a reduction in the percentage of live fetuses/litter for the mice at 1800 and 5000 ppm (95% resorbtions in the 5000-ppm group). Fetal weight and sex ratio in mice were not affected. An increase in the incidence of reduced sternebral ossifications was correlated to the THF concentration although differences between groups were not statistically significant. There were no increases in the incidences of other malformations or variations. These results suggest that THF may be embryotoxic in mice, but if the conceptus survives, development continues in the normal fashion. The NOAEL for maternal toxicity was 1800 ppm in both rats and mice. The NOAEL for developmental toxicity was 1800 ppm in rats and 600 ppm in mice.

7.9.2.6 Neurotoxicity

Rats given intraperitoneal injections of THF reacted with slight confusion and slowness to react that lasted for about 10 minutes at 10 minutes after the injection. Repetition of the treatment the following day showed no further CNS depression. With doses increasing up to 2230 mg/kg, CNS depression lasted about 6 hours. With repeated injections at this concentration, the same CNS depression was observed, the overall condition deteriorated, and death occurred in one animal after the third injection (HSDB 2011).

Werawattanachai et al. (2007) exposed laboratory animals to THF and then evaluated them in a neurobehavioral test. Decreased performance was observed in the righting reflex and the rotarod test. While some of the mechanisms of the THF actions on the CNS appear likely to involve direct or indirect interactions with the GABA-B receptor, some differences in qualitative and quantitative pharmacology suggest other mechanisms are also likely involved in the observed neurobehavioral effects of these selected doses of THF in mice.

7.9.2.7 Genotoxicity

THF is negative in the Ames test, the *E. coli* reverse mutation assay with *E. coli WP 2* up to 20 µL/plate with or without microsomal activation, the Sister Chromatid Exchange assay with CHO-W-B1 at 500-5000 µL with and without microsomal activation, and the micronucleus assay in mice (PubChem 2019g).

THF did not induce unscheduled DNA synthesis in rat hepatocytes (PubChem 2019f).

7.9.2.8 Carcinogenicity

THF is suspected of being carcinogenic. The ACGIH considers THF a confirmed animal carcinogen with unknown relevance to humans (PubChem 2019f).

The NTP conducted a 102-week study by inhalation in male and female rats and mice at exposures of 0, 200, 600, or 1800 ppm, 6 hours/day, 5 days/week. There was some evidence of carcinogenicity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female rats or male mice. There was clear evidence of carcinogenic activity in female mice based on increased incidence of hepatocellular neoplasms (NTP 1998).

7.9.2.8 Ecotoxicology

7.9.2.8.1 Fate and Transport

If released to soil, THF is expected to have very high mobility based upon K_{oc} values of 18 and 23. If released into water, THF is not expected to adsorb to suspended solids and sediment, based upon the K_{oc} values. Volatilization from water or wet soil is expected to be an important fate process based upon this compound's K_H of 7.05 x 10^{-5} atm-m^3/mol. Based upon its vapor pressure, THF may volatilize from dry soil surfaces. If released to air, a vapor pressure of 162 mm Hg at 25ºC indicates THF will exist solely as a vapor in the atmosphere. An estimated BCF of 3 suggests the potential for bioconcentration of THF in aquatic organisms is low (PubChem 2019f).

7.9.2.8.2 Ecotoxicity

No data were found for toxicity in green algae. The ECOSAR model (EPA 2018) predicts a 96-hour EC_{50} of 136mg/L in green algae.

The LC_{50} in *Daphnia* is reported to be 5930 mg/L and >10,000 mg/L for a 24-hour exposure, and the LC_{50} in various species of fish ranges from 2400 mg/L to 5900 mg/L for a 48-hour exposure. The 96-hour LC_{50} in fathead minnow (*Pimephelas promelas*) is 2160 mg/L (PubChem 2019f).

7.9.2.8.3 Degradation/Treatment

Hydrolysis is not expected to be an important environmental fate process since THF lacks functional groups that hydrolyze under environmental conditions. Vapor-phase THF will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals and nitrate ions; the half-lives of these two reactions in air are 21–24 hours and 3 days, respectively (PubChem 2019f).

THF is rapidly degraded by aerobic biodegradation. Using the European Economic Community manometric repirometric method in 22 different laboratories, THF reached a mean of 34% of

theoretical BOD within 28 days. THF is resistant to anaerobic biodegradation. With a primary digesting sludge as an innoculum, the lag period was more than 60 days (HSDB 2011).

7.10 p-Toluenesulfonic acid [PTSA]

7.10.1 General Information

Anhydrous PTSA is a crystalline solid (Budavari 1996). The IUPAC nomenclature is 4-methylbenzenesulfonic acid (PubChem 2019g). Figure 7 illustrates the molecular structure of PTSA.

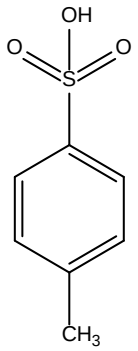

Figure 7. PTSA

7.10.2 Toxicology Data

The primary hazard of PTSA arises from its high acidity.

7.10.2.1 Oral

The acute oral LD_{50} of PTSA is reported to be 1410 mg/kg in the rat, 735 mg/kg in mice, and >316 mg/kg in quail (PubChem 2019g).

No chronic LOAEL data were available. TOPKAT modeling predicts a chronic LOAEL of 60.3 mg/kg-day at high confidence.

7.10.2.2 Inhalation

PTSA may cause respiratory irritation (PubChem 2019g).

No experimental data were found. TOPKAT modeling predicts an acute inhalation LC_{50} in rats of >10 g/m^3-hour at high confidence.

7.10.2.3 Dermal

PTSA may cause skin irritation or corrosion (PubChem 2019g).

7.10.2.4 Ocular

PTSA may cause irritation or serious eye damage (PubChem 2019g).

7.10.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts PTSA will be a developmental or reproductive toxicant at high confidence.

7.10.2.6 Neurotoxicity

No experimental data were found.

7.10.2.7 Genotoxicity

No experimental data were found. TOPKAT modeling predicts PTSA will not be mutagenic in the Ames assay.

7.10.2.8 Carcinogenesis

No experimental data were found. TOPKAT modeling predicts PTSA will not be carcinogenic.

7.10.2.9 Ecotoxicology

7.10.2.9.1 Fate and Transport

PTSA is a strong acid and is completely dissociated and highly soluble in water. It is expected to be highly mobile and may pose a hazard to surface and drinking water. PTSA will volatilize from both water and wet surfaces and is expected to exist in the atmosphere as both a vapor and a particulate. PTSA will not bioaccumulate in aquatic organisms (HSDB 1995).

7.10.2.9.2 Ecotoxicity

No experimental data were found. The ECOSAR (2018) program predicts a 96-hour EC_{50} of 3.88×10^4 mg/L in green algae, a 48-hour LC_{50} of 1.42×10^5 mg/L in *Daphnia,* a 96-hour LC_{50} of 3.17×10^5 mg/L in fish, and a 14-day LC_{50} of 5.59×10^3 mg/L in earthworms.

7.10.2.9.3 Degradation/Treatment

Vapor phase PTSA will react with photochemically-produced hydroxyl radicals with an estimated half-life of 11.8 days. Biodegradation may proceed very slowly if acclimated microorganisms are absent from the bodies of water (HSDB 1995).

8 Discussion

8.1 Compound Summaries

8.1.1 2-Mercaptobenzothiazole

Dermal exposure appears to be the most significant hazard of 2-MBT, both occupationally and from exposure to rubber products. Although the oral and inhalation toxicities of 2-MBT are high, they are considered low-impact since exposure by ingestion or inhalation is considered unlikely, and there is no epidemiological evidence for toxicity via these routes. Genotoxicity is not significant, but there is some evidence of potential carcinogenicity in long-term rodent studies, and 2-MBT is considered a possible human carcinogen (bladder cancer).

Ecotoxicity is reported to be significant, but measured toxicity values do not reflect this. Environmental persistence is expected to be high, with possible adverse effects on bacteria that biodegrade xenobiotics.

8.1.2 Melamine

Accumulation of melamine crystals within the bladder and kidney represents the greatest hazard to animal species. Frank melamine toxicity is relatively low by regular routes of exposure: oral, inhalation and dermal. Occupational hazards are low although melamine is a mild ocular irritant. There are indications that melamine may be a neurological hazard during development, but this is not relevant to adults. Melamine does not represent a genotoxic or carcinogenicity hazard.

High water solubility means melamine will be highly mobile in groundwater. Based on ECOSAR (2018) modeling predictions, melamine is predicted to be low in direct toxicity towards aquatic species.

8.1.3 Formaldehyde

Formaldehyde is considered a probable human carcinogen. Formaldehyde is an acute oral and inhalation hazard, an ocular and dermal irritant, and a likely dermal sensitizer. Developmental and reproductive effects are minimal, and some mild neurological impairment has been noted upon chronic exposure. Health effects of formaldehyde might be mitigated by its extreme reactivity, shortening potential exposures.

Ecotoxicology hazards are moderate overall. Formaldehyde’s high reactivity will reduce environmental exposures.

8.1.4 Pentaerythritol tetrakis (3-mercaptopropionate)

PTT is moderately toxic via ingestion and probably inhalation, and non-toxic dermally. Occupational exposure hazards are low to moderate, with skin sensitization a possible hazard. PTT is anticipated to be only a mild ocular irritant and is not expected to be genotoxic or carcinogenic. Developmental or reproductive toxicity is possible, but predictions are low-confidence.

Lack of environmental mobility limits environmental toxicity. If discharged directly to water, PTT is expected to pose a hazard to organisms at lower trophic levels. Persistence in the environment is expected to be weeks to months.

8.1.5 Sodium dodecyl sulfate

SDS is a relatively non-toxic surfactactant found in many cleaning solutions. In pure form, it is moderately toxic by ingestion or inhalation, and non-toxic dermally. SDS poses a moderate occupational hazard due to dermal and ocular irritation. It is not genotoxic or carcinogenic, and it is not known to be a developmental or reproductive toxicant or a neurological hazard.

SDS is not mobile in the environment; it is moderately toxic toward aquatic species. SDS is susceptible to degradation by aerobic bacteria with a relatively short biological half-life.

8.1.6 Gum arabic

Gum arabic is a non-toxic natural product. Historical use in printing processes led to cases of "printers asthma," but other products that have since been substituted have eliminated this problem (HSDB 2002).

8.1.7 Tetrahydrofuran

THF is a severe ocular hazard, causing both irritation and corrosion depending upon the concentration. THF is moderately toxic via the oral route of exposure. By inhalation and dermal exposure, toxicity is low although dermal irritation and drying are possible. Mutagenicity testing is negative, and the compound is not classified as a human carcinogen.

High solubility and mobility make THF a groundwater transport hazard, but its toxicity toward wildlife species is relatively low. Environmental persistence is moderate.

8.1.8 p-Toluenesulfonic acid

PTSA is a highly soluble, strong acid. Its most significant hazard is to eyes, where it is classified as a strong irritant/corrosive. QSAR modeling indicates possible developmental or reproductive toxicity. Frank toxicity is low to moderate; inhalation and dermal toxicity are essentially nil, and oral toxicity is moderate. PTSA is not believed to be either mutagenic or carcinogenic.

Ecotoxicity is low, but mobility in water is very high. PTSA will not bioaccumulate, and it is biodegradable by aerobic microorganisms.

8.2 Regulations and Standards

8.2.1 2-Mercaptobenzothiazole

The European Commission has set a Threshold Limit Value (TLV) of 3 mg/m^3 for 2-MBT respirable particulates and 10 mg/m^3 for inhalable 2-MBT particulates (PubChem 2019a).

A workplace environment exposure limit for an 8-hour exposure has been established at 5 mg/m^3 on the basis of dermal sensitization (PubChem 2019a).

8.2.2 Melamine

Melamine is considered of low relative toxicity except by direct ingestion, and it is approved by the U.S. Food and Drug Administration (FDA) as an indirect food additive derived from packaging materials. The estimated level of melamine in food resulting from approved uses is less than 15 µg/kg (0.015 ppm) (FDA 2018, HSDB 2012).

In the aftermath of the pet food and infant formula crises, the FDA issued an Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans. This Interim Assessment was based upon the 13-week rat study by Melnick et al. (1984), and applied uncertainty factors for interspecies variability, extrapolating from a LOAEL to a NOAEL, and uncertainty surrounding the presence of melamine analogues, especially cyanuric acid, which affect the formation of urinary crystals, for a combined uncertainty factor of 1000. The maximum tolerated dose for humans older than 3 years of age was calculated to be 0.63 mg/kg-day. Applying assumptions about the weight of the average human and the mass of food consumed daily, this resulted in a Maximum Contaminant Level of 2.5 ppm or 2.5 mg/kg in food. The FDA was unable to establish a safe level of consumption for infants and toddlers (FDA 2012).

Only a month after issuing the Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans, the FDA updated the assessment to include infants because analysis of infant formula samples had revealed that the presence of both melamine and cyanuric acid at the same time, a complicating issue for the first assessment, was found to be uncommon. Accordingly, FDA applied a 10-fold uncertainty factor for infants, but removed the 10-fold factor for presence of multiple analogues. Hence, a Tolerated Daily Ingestion (TDI) level of 0.063 mg/kg-day was set for infants. Applying assumptions about the weight of infants and the quantity of formula consumed daily, a Maximum Contaminant Level of 1.0 ppm melamine in food was established (FDA 2008b).

8.2.3 Formaldehyde

The NIOSH 15-minute Recommended Exposure Limit (REL) is a time-weighted 0.016 ppm, and the OSHA Permissible Exposure Limit (PEL) is a time-weighted 0.75 ppm with a short-term exposure limit of 2 ppm (1 ppm = 1.23 mg/m^3)(NIOSH 2018).

The ACGIH has established a TLV of 0.3 ppm based upon sensitization (PubChem 2019c).

The EPA has established a Federal drinking water guideline of 1000 µg/L. Several states have established more stringent standards, including California, New Jersey, and New Hampshire (100 µg/L), Florida (600 µg/L), and Maine (140 µg/L). Wisconsin and Minnesota enforce at the level of the Federal standard (PubChem 2019c).

The ATSDR has established a chronic inhalation Minimal Risk Level (MRL) of 0.008 ppm (0.010 mg/m^3) based on respiratory effects in humans, and a chronic oral MRL of 0.2 mg/kg-day. The

MRL is an estimate of the daily human exposure that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime (ATSDR 2010b).

The Reference Dose (RfD) for formaldehyde is 0.2 mg/kg-day based on decreased body weight gain and effects on the stomach in rats (PubChem 2019c).

8.2.4 Pentaerythritol tetrakis(3-mercaptopropionate)

No regulations or standards pertaining to PTT were found.

8.2.5 Sodium dodecyl sulfate

No regulations or standards pertaining to SDS were found.

8.2.6 Gum arabic

Gum arabic is GRAS when used in accordance with accepted practices (HSDB 2002).

8.2.7 Tetrahydrofuran

For THF, OSHA has established a PEL of 200 ppm (590 mg/m^3) as an 8-hour time-weighted average (TWA). The NIOSH REL is 200 ppm for a 10-hour exposure, and a 15-minute Short-Term Exposure Limit (STEL) of 250 ppm (735 mg/m^3). The Immediately Dangerous to Life or Health (IDLH) level is 2000 ppm (PubChem 2019).

Based on skin considerations, the ACGIH has set an 8-hour TWA TLV of 50 ppm, and a 15-min STEL of 100 ppm (PubChem 2019).

Several states have adopted drinking water guidelines for THF: Massachusetts (600 µg/L), New Hampshire (150 µg/L), Maine (70 µg/L), Wisconsin (50 µg/L), and Florida (4.6 µg/L) (PubChem 2019f).

8.2.8 p-Toluenesulfonic acid

No regulations or standards pertaining to PTSA were found.

8.3 Conclusions

A cancer hazard is associated with 2-MBT and formaldehyde. While there are data gaps for some of the other compounds in this formulation, most of the hazard is derived from typical occupational concerns, such as dermal and ocular irritation, that are normally addressed via PPE. There are additional issues for some compounds, but there are factors in mitigation. For example, while 2-MBT is classified as highly toxic, it is widely used in industrial rubber products, and there is no epidemiological evidence of serious health issues in humans although workers have been found to be at increased risk of bladder cancer. Formaldehyde represents a potential concern, as it is a likely human carcinogen and also poses hazard for inhalation, oral, and

dermal exposures and moderate dermal, ocular, and neurological effects. The remaining compounds in the formulation are of low to moderate toxicity and are not thought to be a serious exposure concern.

9 Recommendations

Measures should be taken to address some of the data gaps outlined in this report via experimental work, although none of these factors appear critical to acceptance of this formulation. Notably, there is a question regarding the acute oral toxicity of 2-MBT in rats: the value of 100 mg/kg has been reported but is unverified. Little publicly documented experimental information is available for PTT. This shortfall could be addressed as time and resources permit, but is not critical to the current project. There are no significant information shortfalls for the remaining compounds in the formulation.

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; creates a classification process for comparison with defined hazard criteria; and communicates 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 classification of chemicals into various hazard categories based upon their effects and the 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 LD50 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 = millgrams per liter
ppm = parts per million

Table B-2. GHS Skin Corrosion/Irritation

<table>
<tr><th colspan="3">Skin Corrosion
Category 1</th><th>Skin Irritation
Category 2</th><th>Mild Skin Irritation
Category 3</th></tr>
<tr><td colspan="3">Destruction of dermal tissue; visible necrosis in at least one animal.</td><td rowspan="2">Reversible adverse effects in dermal tissue
Draize score: ≥ 2.3, <4.0, or persistent inflammation</td><td rowspan="2">Reversible adverse effects in dermal tissue

Draize score: ≥ 1.5, <2.3</td></tr>
<tr><td>Subcategory 1A
Exposure < 3 minutes
Observation < 1 hour</td><td>Subcategory 1B
Exposure < 1 hour
Observation < 14 days</td><td>Subcategory 1C
Exposure < 4 hours
Observation < 14 days</td></tr>
</table>

Table B-3. GHS Eye Effects

<table>
<tr><th>Category 1: Serious Eye Damage</th><th colspan="2">Category 2: Eye Irritation</th></tr>
<tr><td rowspan="2">Irreversible damage 21 days after exposure

Draize score:
Corneal opacity ≥ 3
Iritis ≥ 1.5</td><td colspan="2">Reversible adverse effects on cornea, iris, conjunctiva

Draize score:
Corneal opacity ≥ 1
Iritis > 1
Redness ≥ 2
Chemosis ≥ 2</td></tr>
<tr><td>Irritant
Subcategory 2A
Reversible in 21 days</td><td>Mild irritant
Subcategory 2B
Reversible in 7 days</td></tr>
</table>

Table B-4. GHS Acute and Chronic Aquatic Toxicity

<table>
<tr><th>Acute Category I
Acute toxicity ≤ 1.00 mg/L</th><th>Acute Category II
Acute toxicity > 1.00 but ≤10.0 mg/L</th><th colspan="2">Acute Category III
Acute toxicity > 10.0 but < 100 mg/L</th></tr>
<tr><td>Chronic Category I
Acute toxicity ≤ 1.00 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500.</td><td>Chronic Category II
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.</td><td>Chronic Category III
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.</td><td>Chronic Category IV
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.</td></tr>
</table>

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

Glossary
Acronyms and Abbreviations

2-MBT	2-Mercaptobenzothiazole
ACGIH	American Conference of Governmental Industrial Hygienists
APHC	U.S. Army Public Health Center
atm-m^3/mol	unit of Henry's Law constant
ATSDR	Agency for Toxic Substances Disease Registry
BCF	bioconcentration factor
BOD	Biological Oxygen Demand
bp	boiling point
°C	degrees Celsius
CAS RN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary
CNS	central nervous system
CPDB	Carcinogenic Potency Database
Cr(VI)	hexavalent chromium
DNA	deoxyribonucleic acid
DOD	Department of Defense
DTIC	Defense Technical Information Center
EC_{50}	effective concentration to achieve 50-percent effect
ECB	European Chemicals Board
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
GD	gestation day
GHS	Globally Harmonized System
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
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% mortality
LC_{LO}	lowest lethal concentration
LD_{50}	dose resulting in 50% mortality
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
n/a	not applicable
ND	no data
NIOSH	National Institute for Operational Safety and Health
nm	nanometer
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Office of Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration

PPE	personal protective equipment
ppm	parts per million
PTSA	p-Toluenesulfonic acid
PTT	pentaerythrytol tetrakis(3-mercaptopropionate)
RDT&E	research, development, testing, and evaluation
REL	Recommended Exposure Limit
SDS	sodium dodecyl sulfate
SERDP	Strategic Environmental Research and Development Program
STEL	Short-term Exposure Limit
TAC	Total Allowable Concentration
THF	tetrahydrofuran
TLV	Threshold Limit Value
TOPKAT	Toxicity Prediction Komputer Assisted Technology
TOXNET	Toxicology Data Network
TWA	time-weighted average
vp	vapor pressure
WHO	World Health Organization