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Toxicology Report No. S.0052729-14
U.S. Army Environmental Technology Acquisition Program
May 2018

Toxicology Assessment for Green, Improved Process to Load Primers
ETAP Work Unit ALR 14-02

Prepared by
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ARIMS designation: 500c

ACKNOWLEDGEMENT

The author would like to acknowledge the support and encouragement provided to this effort by Mr. Erik Hangeland, Director, and Ms. Kimberly Watts, Deputy Director, of the Army Environmental Quality Technology (EQT) Environmental Technology Acquisition Program (ETAP). Dr. John LaScala of the EQT Pollution Prevention Technology Team (P2TT) provided support and encouragement to this project.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
31-05-2018	Technical Report	October 2014-May 2018

4. TITLE AND SUBTITLE
Toxicology Assessment for Green, Improved Process to Load Primers ETAP Work Unit ALR 14-02

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
William S. Eck, Ph.D.

5d. PROJECT NUMBER
ALR 14-02

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
U.S. Army Public Health Center
Toxicology Directorate
8988 Willoughby Road
Aberdeen Proving Ground, MD 21010-5403

8. PERFORMING ORGANIZATION REPORT NUMBER
S.0052729-14

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Research, Development and Engineering Command (RDECOM)
Environmental Technology Acquisition Program (ETAP)
3071 Aberdeen Blvd
Aberdeen Proving Ground, MD 21005-5201

10. SPONSOR/MONITOR'S ACRONYM(S)
RDECOM/ETAP

11. SPONSORING/MONITORING AGENCY REPORT NUMBER

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
The RDECOM ETAP program is dedicated to finding replacements for compounds and formulations within the Army system that pose a hazard to human health and the environment. This Toxicology Assessment addresses a new DBX-1 formulation for primer caps that not only replaces the lead-based primary explosives, but may be applied in an automated fashion, replacing the manual methods currently being employed for filling primer caps and significantly reducing worker exposure and hazard. This formulation is based upon DBX-1 and tetrazene, and assessed to be largely benign, although some data gaps remain. Some additional testing should be carried out, but this formulation represents a great improvement in human health and environmental effects when compared with the current lead-based primer formulations.

15. SUBJECT TERMS
DBX-1, tetrazene, primary explosives, primer caps

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	U/U		William S. Eck, Ph.D.
U	U	U			19b. TELEPONE NUMBER (*Include area code*) 410-436-3980

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Glossary

ACGIH	American Conference of Governmental Industrial Hygienists
BAL	Brochoalveolar lavage
BCF	Bioconcentration Factor
BSI	Brief System Inventory (neurological test)
CEI	Cumulative Exposure Index
CNS	Central Nervous System
EC_{50}	Effective concentration to achieve 50 percent effect
ECHA	European Chemical Agency
EPA	Environmental Protection Agency (US)
FSH	Follicle stimulating hormone
GHS	Globally Harmonized System
GRAS	Generally recognized as safe
IARC	International Agency for Research on Cancer
IC_{50}	Concentration causing 50 percent inhibition
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
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NTP	National Toxicology Program
PI	Post-instillation
PND	Post-natal day
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SCE	Sister chromatid exchange
SHE	Syrian hamster embryo

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Green Improved Process to Load Primers
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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 US Army. Safeguarding the health of Soldiers, civilians, and the environment requires an assessment of alternatives before they are fielded. Continuous assessments begun early in the Research, Development, Testing and Evaluation (RDT&E) process can save significant time and effort during RDT&E, as well as over the life cycle of the items developed. Residues of pyrotechnics, propellants, explosives and incendiaries that were part of mission-essential activities have been found in soil, air, surface and groundwater samples. Remediation of the contaminated areas has cost the DoD millions of dollars and can interfere with training activities.

1.2 Purpose

Primer caps are necessary to initiate the combustion process for all types of munitions. These caps are filled with an impact-sensitive formulation that typically contains both lead azide and lead styphnate. These caps are very small, typically just 2-3 millimeters in diameter and are loaded by hand in a process that has not changed significantly in decades. Workers involved in this process are potentially exposed to quantities of lead-containing materials that could have adverse health effects, as well as hazardous solvent vapors. In addition, the hand application process is outmoded and inefficient. Additionally, Soldiers are increasing exposed to higher concentrations of lead vapors from use of lead-based primers, some at levels that have been shown to adversely affect health. The Army is in the process of eliminating the lead-based primers with lead-free alternatives, and this is the ideal opportunity to update the filling process. The purpose of this project is to develop an automated means of filling these primer caps with a DBX-1 formulation that would reduce human exposure and be a more efficient way of producing these items.

1.3 Conclusions

Overall, this formulation is considered to be of low to moderate toxicity, and is certainly less toxic than the lead compounds that are being replaced. With few exceptions, the compounds involved in the formulation are generally well-understood from a toxicological perspective; specific additional testing is recommended; however, due to poor solubility and reactivity, there are limited *in vitro* testing options for DBX-1. Short-term animal testing may be useful for evaluating genotoxicity; however, there are potential safety issues regarding the preparation and dosing of DBX-1. *In vitro* followed by *in vivo* testing of tetrazine is recommended.

Occupational health risks appear to be low overall, but the formulation probably poses an ecotoxicity hazard, and should therefore not be released into the environment. Ecotoxicity evaluations should be considered if there is the prospect of significant environmental release.

1.4 Recommendations

In vitro toxicity testing is recommended for DBX-1, if feasible; testing of tetrazene is already being undertaken as part of a different requirement. Ecotoxicity testing should be considered.

2 References

See Appendix A for list of references

3 Authority

Funding for this work was provided under Military Interdepartmental Purchase Request No. 1045394, dated 30 Dec 2013. This Toxicology Assessment addresses, in part, the environment, safety and occupational health (ESOH) requirements outlined in Army Regulation (AR) 200-1, Environmental Protection and Enhancement, 1997; AR 40-5, Preventive Medicine, 1990; and AR 70-1, Army Acquisition Policy, 2011; Department of Defense Instruction (DoDI) 4715.4, Pollution Prevention, 1998 and Army Environmental Requirement and Technology Assessment (AERTA) requirement PP-3-02-05, *Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces*, (AERTA 2012). The Sponsor is the Army Environmental Quality Technology (EQT) program, Environmental Technology Acquisition Program (ETAP). The Principle Investigator is Ms. Neha Mehta of the U.S. Army Armament Research, Development and Engineering Center (ARDEC), Picatinny Arsenal, NJ.

4 Background

Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and groundwater. 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 research, development, test and evaluation (RDT&E) process in order to avoid unnecessary costs, conserve physical resources, and sustain the health of our forces and others potentially exposed.

In an effort to support this preventive approach, the 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

Methods used for filling primer caps used in military munitions have not changed since World War II, and involve workers squeegeeing the primer paste over a tray containing empty primer cups. This method is labor-intensive, wasteful of primer chemical formulations and potentially puts workers involved in fulling the caps at risk from both solvent vapors and the explosive nature of the chemical formulations. The objective of this project is to develop an automated process for loading newly-developed lead-free primer formulations, eliminating the problems associated with the current method.

6 Methods

In order to determine the human health and environmental impact of compounds employed in these formulations, it is necessary to correctly identify each compound 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 way of accessing information for 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.

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

The physico-chemical 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 modes 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 (USEPA); the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR); the USEPA 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 (NCBI) and the International Agency for Research on Cancer (IARC). (TOXNET® is a registered trademark of the U.S. National Library of Medicine; DTIC® is a registered trademark of the Defense Technical Information Center.)

Primary references are identified and retrieved using PubMed® and the ProQuest® Research 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

Table 1. Formulation Components and Predicted Products

Chemical Substance	CAS Number
DBX-1	957133-97-1
Antimony trisulfide	1345-04-6
Tetrazene	109-27-3 / 31330-63-9
Barium nitrate	10022-31-8
Aluminum	7429-90-5
Isopropyl alcohol	67-63-0
Methylcellulose	9004-67-5

(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. TOXNET®, ChemIDPlus®, HSDB®, TOXLINE®, and PubMed® are registered trademarks of the U.S. National Library of Medicine; ProQuest® is a registered trademark of ProQuest LLC.

In the absence of published information, QSAR models, such as TOPKAT (BIOVIA 2015), EPI Suites (Estimation Program Interface) 2012, and ECOSAR (Ecological Structure Activity Relationships Predictive Model, Versions 1.11 and 2.0) 2018 may be used to predict toxicity endpoints, physical properties, and ecotoxicity endpoints, respectively, if applicable to the type of molecule under consideration.

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, though the relative proportions of each substance were also factored into the final assessment. In addition, classification in the Globally Harmonized System (GHS; OSHA 2012) is also included for many of these compounds (Appendix B).

7 Results

7.1 Physical and Chemical Properties

Physical and chemical properties are summarized in Table 3. When data were not found, "ND" (no data) is inserted. In some cases the property named is not applicable (“n/a”) to the substance being described. For example, if the compound is a nonvolatile solid or an inorganic salt, vapor pressure, K_{OW}, K_{OC}, and the Henry’s Law constant (K_H) are typically negligible.

7.2 Compound Summaries

Summaries of mammalian toxicity data are collected in Table 4. Assessments of human health and environmental toxicity for each of the formula components are presented in Tables 5 and 6, respectively. Each characterization is generally based on the criteria set forth in Table 2. The final risk characterization also incorporates 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 2. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity (modified from Howe et al. 2006)

	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

Notes:
mg/L - milligrams per liter
LOAEL - lowest-observed adverse effect level
LC_{50} – concentration expected to result in 50 percent lethality to a population of test animals.
mg/kg-d - milligrams per kilogram per day
µg/L - micrograms per liter

7.3 Copper (I) 5-nitrotetrazolate [DBX-1]

7.3.1 General Information

DBX-1 is under evaluation as a replacement for lead azide in primary detonators. A review of available information indicates there are several different molecular representations in the energetics literature for the DBX-1 compound—from monomers (as treated in this Substance Profile) to substituted tetramers. These different isomers likely have different properties; a subject beyond the scope of this Substance Profile at this time, but perhaps worthy of further investigation in labs capable of handling this material. No toxicological information was found in the literature search. This substance profile addresses only the organic anion component of DBX-1; the copper(I) anion is not expected to be the limiting factor for toxicity for this compound.

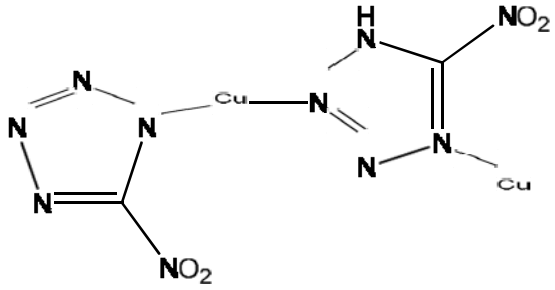

Figure 1: DBX-1 (Structure as determined by single crystal X-ray crystallography (Sabatini and Oyler 2016).

7.3.2 Toxicology Data

7.3.2.1 Oral

TOPKAT modeling predicts an oral LD_{50} of 937 mg/kg with high confidence. The chronic LOAEL is predicted to be 132 mg/kg-day at moderate confidence. These values classifiy DBX-1 as moderately toxic under the APHC system, and Category 4 for acute oral toxicity in the GHS.

In vitro testing of 5-NT using the Neutral Red Uptake test predicts an oral toxicity of 2372 mg/kg (USAPHC 2013).

7.3.2.2 Inhalation

No experimental data were found. TOPKAT modeling predicts an inhalation LC_{50} of 5.5 g/m^3-hour at low confidence. This correlates to low toxicity in the APHC system, and unclassifiable (non-toxic) under the GHS.

7.3.2.3 Dermal

No experimental data were found. TOPKAT modeling predicts DBX-1 is probably not a skin irritant, but is probably a mild sensitizer, at moderate confidence.

7.3.2.4 Ocular

No experimental data were found. TOPKAT modeling predicts DBX-1 is a possible moderate ocular irritant.

7.3.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts DBX-1 will not be a developmental or reproductive toxicant at high confidence.

7.3.2.6 Neurotoxicity

No data were found.

7.3.2.7 Genotoxicity

No experimental data were found. TOPKAT modeling predicts DBX-1 will be mutagenic in the Ames assay at high confidence.

7.3.2.8 Carcinogenicity

No experimental data were found. TOPKAT modeling of DBX-1 for carcinogenicity is indeterminate.

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

With an estimated water solubility of 6.7×10^4 mg/L, 5-nitrotetrazole is highly soluble, and with a log K_{OC} estimated at 0.244, mobility in ground water is expected to be high. DBX-1 has been observed experimentally to dissolve only slowly in water (USAPHC 2014), likely resulting in restricted mobility if released to soil. TOPKAT modeling predicts a vapor pressure of 8.41×10^{-4} mmHg, indicating DBX-1 would be relatively volatile in air and exist as a vapor. This has not been experimentally observed, probably due to the de-facto higher molar mass from the formation of dimers and higher order crystals. The log K_{OW} of -0.76 suggests the tendency to bioaccumulate will be low; the log BCF is estimated to be 0.50, indicating no bioaccumulation.

7.3.2.9.2 Ecotoxicity

No experimental data were found. TOPKAT predicts an LC_{50} in *Daphnia* of 5.3 mg/L at low confidence. No prediction could be made for fathead minnow due to lack of a suitable model.

EPA's ECOSAR program models DBX-1 as a neutral organic with a 96-hour LC_{50} in green algae of 1.61×10^4 mg/L, a 48-hour LC_{50} for *Daphnia* of 9.1×10^4 mg/L, and a 96-hour LC_{50} in fish of 2.27×10^5 mg/L, which is expected to exceed the solubility of the compound. These values indicate DBX-1 is not toxic toward aquatic species.

7.3.2.9.3 Degradation/Treatment

DBX-1 dissolves only slowly in water. When solubilized with a co-solvent such as DMSO and then transferred to water, degradation occurs rapidly producing a flocculent precipitate (USAPHC 2014).

DBX-1 is predicted by EPI Suite modeling to be poorly removed by wastewater treatment processes, however its relative insolubility in water will likely make it easily removed via precipitation.

7.4 Antimony trisulfide [Sb_2S_3]

7.4.1 General Information

Sb_2S_3 is a gray, lustrous crystalline solid that occurs naturally as the mineral stibnite. There is also a red modification. It is used in pyrotechnics and explosives, Bengal fires, and manufacture of ruby glass and matches, and as a paint pigment (Budavari 1996). Synonyms include sulfanylidene(sulfanylidenestibanylsulfanyl)stibane (IUPAC name), stibnite, black antimony, needle antimony, orange antimony and crimson antimony, among others (PubChem 2018a).

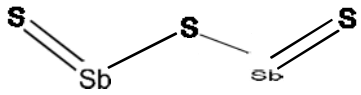

Fig. 2. Sb_2S_3

7.4.2 Toxicology Data

7.4.2.1 Oral

The acute oral LD_{50} in rats is reported to be more than 2000 mg/kg (Sigma-Aldrich 2016); substances with LD_{50}s of 2000 mg/kg or greater are considered non-toxic.

Subacute exposure can result in profuse salivation, nausea, vomiting and diarrhea (HSDB 2005a).

In an 8-week study involving rats, test animals received 6 mg/kg body weight for either 8 or 12 weeks. Kidney Malpighian corpuscles showed distortion, destruction, and congestion of glomerular tuft, vacuoles in the glomeruli, peritubular hemorrhage, obliteration of Bowman's space, and thickening with irregularity of Bowman's membrane. Proximal convoluted tubules demonstrated patchy loss of their brush border, thickening of the basement membrane with loss of its basal infoldings, disarrangement of the mitochondria, pleomorphic vacuoles in the cytoplasm, apical destruction of the cells, apical migration of nuclei, and absence of microvilli (Rashedy et al. 2013).

7.4.2.2 Inhalation

No inhalation LC_{50} could be found; QSAR modeling cannot be performed due to the inorganic nature of the compound.

Respiratory exposure can result in rhinitis with anosmia (inability to perceive odor), tracheobronchitis, pulmonary edema with dyspnea, and sometimes late bronchopneumonia (HSDB 2005a).

Sudden deaths due to heart disease were examined in workers in a plant using antimony trisulfide in the manufacture of grinding wheels. In the workers studied, 14 of 113 had blood pressures in excess of 140/90 and 37 of 75 showed significant changes in EKGs. Ulcers were detected in the

exposed at a rate of 63 per 1000, as compared to 15 in 1000 in the total plant population. Although use of antimony trisulfide was discontinued, EKG changes persisted in 12 of 665 workers (HSDB 2005a).

7.4.2.3 Dermal

The dermal LD_{50} in rats is reported to be greater than 2000 mg/kg (Sigma-Aldrich 2016).

Skin contact may produce erythema and pain (HSDB 2005a).

7.4.2.4 Ocular

Subacute exposure to Sb_2S_3 can result in painful conjunctivitis, photophobia, lacrimation and corneal opacity (HSDB 2005a).

7.4.2.5 Development and Reproduction

No experimental data were found. Antimony has been found to cause premature births and spontaneous abortions in women, along with growth retardation in children. Russian studies have suggested that workers exposed to antimony have shown sexual disfunction in males and increased incidence of gynecological problems in females (HSDB 2005a).

Male rats have shown reduced quantities of spermatogenic epithelial cells and inability to fertilize healthy females. Female rats have shown altered reproductive function and sex life (HSDB 2005a).

7.4.2.6 Neurotoxicity

Subacute exposure can result in giddiness, headache, vertigo, amnesia, confusion and unconsciousness. Acute exposure can result in sudden collapse and unconsciousness and death from prompt respiratory paralysis (HSDB 2005a).

7.4.2.7 Genotoxicity

Mutagenicity and cytotoxicity were seen in a *Salmonella* mutagenicity bioassay study, but it is noted that over 70 percent of the samples were contaminated with bacteria and fungi, calling these results into question. Trivalent antimony has induced DNA damage in bacteria (HSDB 2005a).

7.4.2.8 Carcinogenicity

There is inadequate evidence for carcinogenicity of antimony sulfide in humans, but limited evidence in experimental animals (PubChem 2018a).

7.4.2.9 Ecotoxicology

7.4.2.9.1 Fate and Transport

Sb_2S_3 has relatively low solubility, but over time may release the Sb^{3+} ion, posing a transport hazard in groundwater and potentially surface and drinking water. Partition to the atmosphere from water or wet surfaces is unlikely due to the intrinsic chemical nature of the compound. Any Sb_2S_3 found in the atmosphere will likely be present in particulate form.

7.4.2.9.2 Ecotoxicity

No experimental data were found.

A supplier Safety Data Sheet indicates Sb_2S_3 is classified in Category II for both acute and chronic aquatic toxicity under the GHS with long-lasting effects, although no data were given (Sigma-Aldrich 2016).

7.4.2.9.3 Degradation/Treatment

No data on degradation or treatment of Sb_2S_3 could be found; the most likely route of degradation is hydrolysis in acidic environments, with subsequent release of H_2S.

7.5 Tetrazene [TTZ]

7.5.1 General Information

TTZ is a colorless to pale yellow amorphous fluffy solid (Olin 2015). There is a tautomeric form where there is a double bond between the 5-carbon on the tetrazole ring and the first nitrogen in the side chain. The molecule typically has a single water of hydration that is associated with it. Synonyms include TTZ, tetracene, 1-(5-tetrazolyl)-4-guanyltetrazene hydrate, guanyl nitrosoaminoguanyltetrazene, and 4-(1H-tetrazol-5-yl)-3-tetrazene-2-carboximidamide monohydrate.

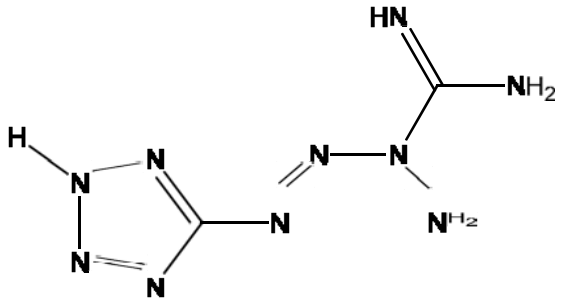

Fig. 3. TTZ

7.5.2 Toxicology Data

7.5.2.1 Oral

No experimental data were found. TOPKAT modeling predicts an oral LD_{50} of 1100 mg/kg at high confidence and a chronic LOAEL of 220.5 mg/kg-day at moderate confidence. This will classify TTZ as moderately toxic in the APHC system, and in GHS Category 4 for acute oral toxicity. The manufacturer's SDS also indicates tetrazene is classified in GHS Category 4 (Olin 2015).

7.5.2.2 Inhalation

The manufacturer's SDS indicates tetrazene is classified in GHS inhalation Category 4 for dust/mist, but provides no quantitative information (Olin 2015).

TOPKAT modeling predicts an inhalation LC_{50} of 0.626 g/m^3-hour at moderate confidence. Due to low vapor pressure, TTZ is expected to exist in the atmosphere as a dust or particulate; this LC_{50}

value places TTZ in the moderately toxic category in the APHC system, and in GHS Category 3 for acute inhalation toxicity.

7.5.2.3 Dermal

No experimental data were found. TOPKAT modeling predicts TTZ to be a possible dermal irritant and a probable sensitizer. The manufacturer's SDS reports no data available for sensitization (Olin 2015).

7.5.2.4 Ocular

The manufacturer's SDS indicates tetrazene is a GHS Category 2 eye irritant, meaning it has reversible adverse effects (7 to 21 days) on the cornea, iris, or conjunctiva of the eye (Olin 2015).

7.5.2.5 Development and Reproduction

The manufacturer's SDS report TTZ is not known to cause developmental or reproductive effects (Olin 2015). TOPKAT modeling predicts TTZ will not be a developmental or reproductive toxicant at moderate confidence.

7.5.2.6 Genotoxicity

The manufacturer's SDS reports TTZ is not known to be mutagenic (Olin 2015). TOPKAT modeling predicts TTZ will be mutagenic in the Ames test at low confidence.

7.5.2.7 Carcinogenicity

TOPKAT modeling of TTZ for carcinogenicity is indeterminate. The manufacturer's SDS indicates TTZ is not listed as a carcinogen by the National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), Occupational Health and Safety Administration (OSHA), the American Conference of Governmental Industrial Hygienists (ACGIH), or the Environmental Protection Agency (EPA).

7.5.2.8 Ecotoxicology

The manufacturer's SDS indicates TTZ has not been evaluated for environmental toxicity or fate and transport or bioaccumulation (Olin 2015).

7.5.2.8.1 Fate and Transport

If released to soil or water, TTZ is assessed to present a significant hazard of groundwater transport due to high water solubility and low adsorption to organic matter, presenting a probable hazard to surface and drinking water. Partitioning to the atmosphere from wet or dry surfaces is unlikely due to the very small value of the Henry's Law constant and vapor pressure. There is little risk of bioaccumulation due to the small value of the log Kow.

7.5.2.8.2 Ecotoxicity

No experimental data were found. TOPKAT modeling predicts an EC_{50} in *Daphnia* of 1600 mg/L at low confidence; no suitable model was available to make a prediction for fathead minnows.

EPA's ECOSAR program models TTZ as an aliphatic amine. The predicted 96-hour EC_{50} in green algae is to be 6.82 x 10^4 mg/L, the predicted 48-hour LC_{50} in *Daphnia* is 2.02 x 10^4 mg/L, and the predicted 96-hour LC_{50} in fish is 3.46 x 10^5 mg/L. All values indicating low toxicity in both the APHC and GHS systems.

7.5.2.8.3 Degradation/Treatment

EPI Suite 4.11 modeling predicts TTZ will not be readily biodegradable, with environmental persistence of days to weeks.

TTZ is predicted to be poorly removed (<2 percent) by physical wastewater treatment processes, primarily by sludge adsorption.

7.6 Barium nitrate [$BaNO_3$]

7.6.1 General Information

The primary industrial use of barium nitrate is in the manufacture of barium oxide (BaO), in green flares, and in signal lights. Historically, it was used in the vacuum tube industry to remove oxygen from the body of the tubes. Barium ion competes with calcium in the body, leading to accumulation in bone and interference with calcium-mediated neurotransmission.

7.6.2 Toxicology Data

7.6.2.1 Oral

Toxicity of barium compounds is directly related to their solubility. Since barium nitrate is relatively soluble, it is also one of the more toxic species of barium salts. The kidney appears to be the most sensitive target organ resulting from repeated ingestion of soluble barium salts (IRIS 2005). In the critical study conducted by the National Toxicology Program (NTP 1994), chemical-related nephropathy was observed in both male and female mice following chronic or subchronic drinking water exposure to barium chloride, which may be considered comparable to barium nitrate for toxicological purposes. Lesions observed included tubule dilatation, renal tubule atrophy, tubule cell regeneration, hyaline cast formation, multifocal interstitial fibrosis, and presence of crystals, primarily in the lumen of the renal tubules (IRIS 2005).

At the molecular level, barium ion, which has very nearly the same ionic radius as potassium ion (136 picometers (pm) vs. 138 pm; Dean 1992), blocks the ion-conducting pore of potassium channels. Blockage of the channel from both the inside and outside of the membrane was evaluated by Taglialatela and coworkers (Taglialatela et al. 1993). Barium ion inside the cell blocked the wild-type open channel with high affinity (K_d = 13 µmol/L). Blockade involved more than one site, was voltage dependent, and increased at more positive potentials. Barium ion external to the cell caused a low affinity ($K_d \approx$ 30 millimol/L) and voltage-independent block of the open DRK1 channel.

Barium ion interference with potassium ion regulation has serious consequences that manifest as hyperkalemia, hypokalemia, cardiotoxicity, neurotoxicity, hypertension, and disturbance of muscle function. Clinical symptoms associated with barium (nitrate) overdose include hypokalemia, arrhythmias, muscular weakness and paralysis, often requiring respiratory support. In a case report on a 22-year-old male who presented with diarrhea, vomiting and cardiac arrthymias from ingesting barium nitrate, the attending physicians reported the symptoms were not relieved by potassium infusion, but were alleviated after hemodialysis (Bahlmann et al. 2005).

There is conflicting evidence whether or not barium exposure may lead to hypertension. While hypertension has been observed in selected animal studies, it appears this is likely due to inadequate calcium, and perhaps other minerals, in the diet. There is some evidence that reduced dietary calcium is a risk factor for hypertension in humans (McCarron et al. 1984), so marginal calcium nutrition could be adversely affected by the presence of barium. Acute hypertension has been observed in humans following accidental or intentional ingestion of soluble barium salts (CDC 2003, Downs et al. 1995).

7.6.2.2 Inhalation

Only one study relating to inhalation of soluble barium salts was found. Guinea pigs were exposed to repeated doses of 250-300 mg barium nitrate/m^3 via inhalation over a 6-month period. X-rays revealed nodular shadows on the lungs within 1 day of exposure. These abnormalities progressed with time and by 8 months, small shadows appeared diffusely throughout the lungs. Nodules developed around the dust particles, and marked, dose-related histological changes were seen after 8 months. Inhalation exposure also caused significant lung changes, including cellular infiltration, hypertrophy, and edema (Rumyantsev 1963).

7.6.2.3 Dermal

Barium nitrate is a skin irritant (HSDB 2005b).

7.6.2.4 Ocular

Barium nitrate is an eye irritant (HSDB 2005b).

7.6.2.5 Development and Reproduction

No data were found.

7.6.2.6 Genotoxicity

Barium nitrate was negative in all strains of *S. typhimurium* regularly used in the Ames assay, with or without S-9 activation (CCRIS 1993).

7.6.2.7 Carcinogenicity

Barium nitrate is not classifiable as a human carcinogen (HSDB 2006).

7.6.2.8 Ecotoxicology

7.6.2.8.1 Fate and Transport

Because of its high water solubility, barium nitrate is expected to transport in ground water. The global average concentration of barium(II) in surface freshwaters is 60 µg/L (Fritz et al. 1992).

Asiatic clams (*Corbicula fluminea*) have demonstrated the ability to remove soluble barium(II) from their aqueous environment, with deposition of insoluble barium sulfate on the inner surface of their shells. No measurements of barium concentration in the soft tissue of the clams was made (Fritz et al. 1992).

7.6.2.8.2 Ecotoxicity

Tatara and coworkers (1998) tested barium(II) toxicity in *Caenorhabditis elegans* as part of a study whose goal was to develop a QSAR equation to predict the toxicity of metal ions based upon their Microtox assay response. The experimental LC_{50} for barium was determined to be 2.80 mM.

Jones (1939) studied the toxicity of various cation salts to the stickleback fish (*Gasterosteus aculeatus* L.). Barium nitrate was found to have a toxicity limit of 400 mg/L (2.90 mM).

Jones (1940) attempted to extend the study in the paragraph above by using the planarian *Polycelis nigra.* He was unsuccessful in determining a toxicity limit for barium(II) in this animal because of extreme variability in the response, finding that over a concentration range of 300 to 60 mg Ba/L, some animals died in all solutions, some survived the 300 mg/L solution for over 4 days, while some died in less than 24 hours in the 60 mg/L solution. Jones concluded that the neurological impact of barium(II) ions on the nervous system of the worm was interfering with toxicity determination. Worms placed in barium nitrate or barium chloride solutions were observed to quickly begin performing convulsive movements, the body alternately expanding and contracting with great energy, accompanied by swelling of the epidermis to the point that the worms' coloring was affected followed by rupture of the epidermis and prolapse of internal tissues.

Effects of barium ions on the soil invertebrate *Enchytraeus crypticus* were investigated by Kuperman and coworkers (ECBC 2002a) using the Enchytraeid Reproduction Test. Barium(II) did not significantly affect adult *E. crypticus* survival up to 1798 mg/kg; for juvenile animals, a bounded NOEL for survival was determined at 433 mg/kg; the EC_{50} for juvenile production was 947 mg/kg.

Effects of barium ions on the earthworm *Eisenia fetida* were investigated by Simini and coworkers (ECBC 2002b) using the cocoon production and survival test. Cocoon production was a more sensitive endpoint than survival. The bounded NOEC for cocoon production was 258 mg Ba/kg; compared to NOEC for survival of 1348 mg Ba/kg.

Effects of barium ions on the soil invertebrate *Folsomia candida* were investigated by Phillips and coworkers (ECBC 2002c) using the Folsomia Reproduction test. For adult and juvenile animals, a bounded NOEL for survival was determined at 211 mg/kg; the EC_{50} for juvenile production was 478 mg/kg.

7.6.2.8.3 Degradation/Treatment

Being an element, barium is not subject to degradation. Conversion to an insoluble compound, such as barium sulfate, is the most likely environmental fate.

7.7 Aluminum [Al]

7.7.1 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 combustion 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 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 hypothesis that aluminum might be

involved in the development of Alzheimer's Disease was first advanced in the 1980's (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).

7.7.2 Toxicology Data

7.7.2.1 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). Users of aluminum-containing medications that have normal kidney function can ingest much larger amounts of aluminum than in the diet, possibly as much as 12-71 mg Al/kg-day 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 underestimates (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 in a different study by the same group of investigators at 330 mg Al/kg-day (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. 1992). 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).

7.7.2.2 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; 8 months later he was dead. Of 27 workers in this plant, 2 died and 4 had radiological changes on X-rays.

McLaughlin et al. (1962) described death of a male exposed to aluminum flake powder. Prior to death, the man exhibited memory loss, speech difficulties, convulsions, weakness, 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.

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.

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; Drew et al. 1974) 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 and 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 had 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 percent increased the 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 percent increase in lung-to-body weight ratio was observed at in guinea pigs (Stone et al. 1979).

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, the percentage of membrane proteins, activities of Na/K-ATPase, $Mg2^+$-ATPase, $Ca2^+$-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).

7.7.2.3 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).

7.7.2.4 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.

7.7.2.5 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 percent 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, luteinizing hormone (LH), and follicle stimulating hormone (FSH)., as well as testicular weight, antioxidant enzyme gene expression and activities, reduced glutathione, zinc, cyclic adenosine-3',5'-phosphate (cAMP) contents, and the number of Leydig cells, along with 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 better than fish oil regarding oxidative and nitrosative stress, Zn deficiency, and Al overload. However, fish oil showed more pronounced effects than CoQ10 on hormoones, 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, 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 are 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).

7.7.2.6 Genotoxicity

Although aluminum complexes with DNA, particularly at lower pH's, *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).

7.7.2.7 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 US Department of Health and Human services 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 and Mitchener 1975a, 1975b). The incidence of “lymphoma leukemia” was significantly increased (10/41 versus 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 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 Department of Health and Human Services and the EPA have not yet evaluated the human carcinogenic potential of aluminum.

7.7.2.8 Ecotoxicology

7.7.2.8.1 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).

7.7.2.8.2 Ecotoxicity

Available data suggest that aluminum is low in toxicity. Many aquatic species have been used in toxicity assays, as were many forms of aluminum, including oxides (USEPA 2018). 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 and 95 percent confidence intervals were 69.82 mg/L (61.82-80.54) for 24 hours, 55.85 mg/L (48.45-66.89) for 48 hours, and 50.23 mg/L (40.96-64.32) 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*, a few ferns, *Symplocos*, and *Orites*. 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).

7.7.2.8.3 Degradation/Treatment

As an element, aluminum is not subject to environmental degradation. It can, however, 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.

7.8 Isopropyl alcohol [IPA]

7.8.1 General Information

IPA is a volatile, colorless liquid with a sharp musty odor. Vapors are heavier than air and mildly irritating to the eyes, nose, and throat. Used in making cosmetics, skin and hair preparations, pharmaceuticals, perfumes, lacquer formulations, dye solutions, antifreezes, soaps and window cleaners. Sold commercially as a 70 percent solution in water (PubChem 2018b). Synonyms include propan-2-ol (IUPAC name), 2-propanol, isopropyl alcohol, rubbing alcohol, and isopropanol. 1 ppm = 2.46 mg/m^3.

7.8.2 Toxicology Data

IPA and ethyl alcohol have been used as low-level disinfectants in healthcare settings for many years. Recent studies have found that ethyl alcohol inhibits protein synthesis in *E. coli* by direct effects on RNA polymerase and that 60-70 percent solutions have *in vitro* efficiency against murine noroviruses, Ebola viruses, and several corona viruses; IPA may function in a similar way (Boyce 2018).

7.8.2.1 Oral

According to clinical experience, IPA is more toxic than ethyl alcohol but less toxic than methanol. Its acute potency as a CNS depressant is about twice that of ethanol. A single lethal dose for humans is about 250 mL, although as little as 100 mL can be fatal (PubChem 2018b).

The oral LD_{50} in rats is reported to be between 4710 and 5840 mg/kg. The oral LD_{50} in mice is reported to be 3600 mg/kg to 4475 mg/kg; in rabbits it is 6410-7990 mg/kg, and in dogs 4797 to 4830 mg/kg (HSDB 2012).

7.8.2.2 Inhalation

Vapors of IPA are mildly irritating to the nose and throat. The lowest published toxic concentrations in humans are 35 ppm for 4 hours, 150 ppm for 2 hours, and 3000 ppm for 6 minutes (PubChem 2018b).

The inhalation LC_{50} in the rat is reported to be 53 mg/L for a 2-hour exposure, 72.6 mg/L for a 4-hour exposure, and 51.04 mg/L for an 8-hour exposure (HSDB 2012).

The lowest published LC_{50}s are 53,000 mg/m^3 in mice and 12,800 ppm for a 3-hour exposure, also in mice. The comparable numbers in rats are 72,600 mg/m^3 and 16,000 ppm for an 8-hour exposure (PubChem 2018b).

Biological effects of a single exposure to moderate or high concentrations of 2-propanol were investigated in Sprague-Dawley rats. Acute toxicity (LC_{50}, 8-hour exposure) found to be 19,000 ppm (17,380-20,760 ppm) for females and 22,500 ppm (19,200-26,400 ppm) for males. Determination of blood levels of 2-propanol and its metabolite, acetone, was carried out during and after a single 4-hour exposure (Concentration range: 500 to 8000 ppm). The amount of acetone

and IPA was directly related to the various air concentrations of alcohol inhaled. Increase of exposure time to 8 hours enhanced considerably the amount of blood acetone which could be determined even 20 hours after exposure. Histopathological examination of rats exposed to high levels of IPA shows typical lesions of chemical pneumonitis and pulmonary edema accompanied by foamy vacuolization of liver cells and severe focal cytoplasmic degradation (Laham et al. 1980).

Ohashi et al. (1988) evaluated the recovery of the nasal mucosa of the guinea pig after exposure to a concentration of 400 ppm IPA. At this dose level, the test animals recovered from tissue degeneration in about 2 weeks. However, at a higher dose (5500 ppm) the recovery period exceeded 2 weeks, suggesting workers exposed to higher concentrations will need longer recovery periods.

7.8.2.3 Dermal

The rabbit dermal LD_{50} is reported to be 12,800-12,870 mg/kg (HSDB 2012).

Long-term exposure to IPA defats the skin, which may cause dryness and cracking (PubChem 2018b).

Skin absorption is a significant factor in IPA toxicity. Twelve rabbits (2-2.6 kg) were divided into 4 groups of 3 each. Groups 1 and 2 were given isopropyl alcohol, 2 and 4 mL/kg respectively, by gavage. Groups 3 and 4 were placed in an inhalation chamber with group 3 having a towel soaked with isopropyl alcohol applied to the chest. Group 4 had a similar towel placed on the chest but with a plastic layer to preclude skin contact. Average blood levels (mg/dL) of isopropanol/acetone were then measured over 4 hours. Oral absorption produced the highest levels of isopropyl alcohol and acetone, followed by inhalation and dermal. Inhalation alone was of little significance. Acetone levels continued to rise even as isopropyl levels fell following oral exposure. With the inhalation plus skin absorption group, both isopropyl and acetone levels continued to rise throughout the 4 hour time period (Martinez et al. 1986).

7.8.2.4 Ocular

Vapors of IPA are mildly irritating to the eyes (PubChem 2018b).

7.8.2.5 Development and Reproduction

The weight of evidence suggests that isopropanol can cause decreases in postnatal pup survival following oral gavage administration of 1000-1200 mg/kg-day to the dams. The NOAEL for this endpoint with oral gavage administration was 700 mg/kg-day. Indications of maternal toxicity were also an important predictor for decreased postnatal survival. Decreased postnatal pup survival was also noted in the drinking water studies with isopropanol with a LOAEL of 2278 mg/kg-day and a NOAEL of 1947 mg/kg-day (Faber et al 2008).

In a rat developmental study, female Sprague-Dawley rats were dosed by oral gavage with either 0, 400, 800, or 1200 mg/kg IPA during gestation days 6 to 15. Mortality was observed in the mid- (4 percent) and high-dose (8 percent) animals and reduced maternal gestation weight gain on gestational days 0 to 20 associated with significantly reduced gravid uterine weight were noted in the high-dose animals. Fetal body weights were reduced at 800 and 1200 mg/kg. No adverse maternal or developmental effects were noted at 400 mg/kg. No teratogenic effects were noted at any dose tested (HSDB 2012).

7.8.2.6 Neurotoxicity

While the mechanism of action of IPA has not been fully elucidated, brain stem depression is thought to be the predominant mechanism. While the clinical effects are thought to be mostly due to IPA, acetone (a metabolite) may also contribute. The major features of severe poisoning are due to CNS and respiratory depression, shock, and circulatory collapse (Slaughter et al 2014).

A young woman developed an acute sensori-motor axonal polyneuropathy after walking barefoot for several hours on carpets soaked by a disinfectant containing isopropanol. The persistence and severity of symptoms raised the possibility of her neuropathy being partly related to immunizations she received 1 month earlier. The occurrence shortly after contact, however, strongly suggested responsibility of the dermal isopropanol exposure. This case being, to the authors' knowledge, the second reported; peripheral nerve toxicity appears possible in adults on prolonged topical exposure, probably in susceptible individuals (Rajabally and Mortimer 2004).

7.8.2.7 Genotoxicity

IPA tested negative in the Ames mutagenicity test, sister chromatid exchange test, micronuclei in mice, and aneuploidy in *Neurospora crassa* (HSDB 2012).

7.8.2.8 Carcinogenicity

There is no evidence for carcinogenicity in humans (HSDB 2012).

7.8.2.9 Ecotoxicology

7.8.2.9.1 Fate and Transport

If released to soil, IPA is expected to have a high mobility in groundwater and pose a hazard to surface and drinking water based upon miscibility with water and a low logKoc value. Volatilization from water or wet or dry surfaces is expected to be a significant fate process. IPA will exist in the atmosphere exclusively as a vapor. An estimated BCF of 3 suggests the potential for bioaccumulation is low (HSDB 2012).

7.8.2.9.2 Ecotoxicity

The LC_{50} for the protozoa *Spirostomum ambiguum* was determined to be 116 mmol/L (6970 mg/L) for a 24- hour exposure and 119 mmol/L (7150 mg/L) for a 48-hour exposure. LC_{50} for a 24-hour exposure of *Daphnia magna* was determined to be 10,000 mg/L. The LD_{50} for fathead minnows (*Pimephales promelas*) for a period of 48-, 72-, or 96-hours was 11,130 mg/L. Other fish species tested had comparable LD_{50} values (HSDB 2012). IPA is essentially non-toxic to aquatic species.

7.8.2.9.3 Degradation/Treatment

Biodegradation is expected to be an important fate process based upon the results of microbial screening tests. Vapor phase IPA will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with a half-life of about 3.2 days (HSDB 2012).

7.9 Methylcellulose [MC]

7.9.1 General Information

MC is a white granular solid medically classified as a bulk-forming laxative (i.e., it absorbs water and increases in volume accordingly) and is used in patients with anorectal conditions, diarrhea, constipation, gastrointestinal disorders, hypercholesterolemia, and to regulate colostomies. Non-medical uses include as a thickener and as a component of adhesives in food packaging applications. MC has a large number of commercial names (HSDB 2002).

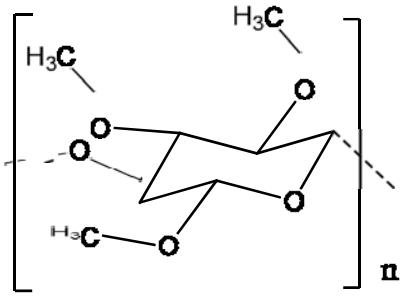

Fig. 4. MC

7.9.2 Toxicology Data

Systemic toxicity is unlikely, as MC is not absorbed from the gastrointestinal tract (HSDB 2002).

7.9.2.1 Oral

MC is practically non-toxic; the probable lethal oral dose in humans is greater than 15 g/kg. Large doses may produce nausea, vomiting, abdominal pain, and diarrhea, and may pose a risk of esophageal obstruction (HSDB 2002). In rats, oral exposure to nitrocellulose only appears to be toxic when treatment levels exceed 10 percent of the normal diet Ellis et al. (1976). The etiology of death observed at this concentration appears to be due to intestinal blockage rather than nitrocellulose toxicity.

7.9.2.2 Inhalation

Occupational asthma, dermatitis, and urticarial have been reported in workers exposed to the dust; severe exposure may lead to aspiration pneumonitis (HSDB 2002).

7.9.2.3 Dermal

MC is non-toxic to skin. MC films are used in manufacture of bandages (HSDB 2002).

7.9.2.4 Ocular

MC is non-irritating to ocular tissue and can be used for long periods without causing damage to the eye (HSDB 2002).

7.9.2.5 Development and Reproduction

No information was found. MC is not anticipated to be a developmental or reproductive toxicant as it is not absorbed.

7.9.2.6 Genotoxicity

No information was found. MC is not anticipated to be genotoxic.

7.9.2.7 Carcinogenicity

No information was found. MC is not anticipated to be carcinogenic.

7.9.2.8 Ecotoxicology

7.9.2.8.1 Fate and Transport

MC is a high molecular weight molecule, so solubility is limited by the concentration and temperature. Gels will form at high concentrations inhibiting mobility. MC is insoluble above 50ºC, so ambient water temperatures are not likely to support significant environmental mobility. Partition to the atmosphere will not occur due to high molecular weight. Bioaccumulation is not anticipated because MC cannot be incorporated into tissue, again because of molecular weight.

7.9.2.8.2 Ecotoxicity

No data were found for green algae. The 48-hour EC_{50} for water flea (*Ceriodaphnia dubia*) is 87.26 mg/L; the 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) is greater than 20 g/L (USEPA 2018).

MC had no significant effect on either corn (*Zea mays*) or beans (*Phaseolus vulgaris*) after a 56-day exposure at up to 6.14 g/1.8 kg soil (USEPA 2018).

7.9.2.8.3 Degradation/Treatment

No information was found. As a cellulose derivative, MC is expected to not be subject to biodegradation in aquatic environments. MC might be degradable in terrestrial environments by white rot fungi or similar organisms, but no information was found.

MC is probably easily removed from waste streams by wastewater treatment plants due to its temperature-dependent solubility and tendency to agglomerate to form gels.

8 Discussion

8.1 Compound Summaries

8.1.1 DBX-1

No experimental toxicological information is available for DBX-1. QSAR modeling predicts that DBX-1 will be moderately toxic by the oral route of exposure, dermal and ocular hazard are also predicted to be moderate based upon skin sensitization and ocular irritation predictions. Modeling predicts DBX-1 will be mutagenic in the Ames assay, but this should be experimentally confirmed.

Ecotoxicity is low across prospective receptors, and transport in the environment will be limited by solubility. Degradation of DBX-1 is likely to occur on solubilization, and release of copper ions may pose a hazard to algal species with subsequent impact on higher trophic levels, however this is not expected to be a serious issue unless large quantities of DBX-1 are released to the environment.

8.1.2 Antimony trisulfide

Antimony trisulfide is a relatively insoluble material that does not appear to be acutely toxic, but which can induce serious and potentially long-lasting systemic effects. Sb_2S_3 is non-toxic via ingestion or dermal exposure, and is not considered to be carcinogenic.

No ecotoxicity data could be found, but available information indicates Sb_2S_3 should not be released to the environment.

8.1.3 Tetrazene

TTZ is assessed to have low to moderate oral, inhalation, ocular and dermal toxicity, posing a moderate hazard in an occupational health environment, primarily due to possible dermal sensitization. QSAR modeling predicts TTZ will not be a developmental or reproductive toxicant, but may be mutagenic in the Ames test; the carcinogenicity prediction is indeterminate.

Ecotoxicity predictions are for low toxicity. Mobility in groundwater is expected to be high, with moderate environmental persistence. Bioaccumulation is not expected to be a hazard.

8.1.4 Barium nitrate

The primary target organ for toxicity of soluble barium is the kidney. Toxicity by standard routes of exposure; however, is relatively low, it is not a developmental or reproductive toxicant, or genotoxic/carcinogenic. Occupational hazards are relatively low if standard chemical handling procedures and equipment are employed.

As toxicity of barium salts is directly related to their solubility, release of barium nitrate to the environment is to be avoided. However, toxicity toward aquatic and soil-dwelling animals is relatively low.

8.1.5 Aluminum

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.

8.1.6 Isopropyl alcohol

IPA has low toxicity by all routes of exposure. It is a mild ocular irritant; defatting of the skin with subsequent penetration may occur upon prolonged exposure. IPA is neither genotoxic or carcinogenic.

Ecotoxicity is also low, and persistence in the environment will be limited by biological degradation and atmospheric hydrolysis.

8.1.7 Methylcellulose

MC is essentially non-toxic by all routes of exposure. It is not expected to pose a hazard to humans or wildlife.

8.2 Regulations and Standards

8.2.1 DBX-1

DBX-1 is a primary explosive and is subject to transportation restrictions. While mutagenicity appears to be the primary concern, because DBX-1 is a high-nitrogen organometallic compound that is poorly handled by contemporary QSAR models, it is also recommended that *in vitro* testing also be performed for acute toxicity (Neutral Red Uptake assay) and aquatic toxicity (luminescent bacteria test) as a preliminary to *in vivo* testing.

8.2.2 Antimony trisulfide

NIOSH and OSHA have established a 10-hour TWA exposure limit of 0.5 mg/m^3; the ACGIH has established the same exposure limit for an 8-hour time-weighted exposure (PubChem 2018a).

The EPA Office of Water has established an exposure limit of 6 µg/L measured as antimony. State standards are 14 µg/L in Arizona, 6 µg/L in Minnesota, and 3 µg/L in Maine (PubChem 2018a).

Under the provisions of section 307(a)(1) of the Clean Water Act, antimony sulphide is a toxic pollutant and subject to effluent limitations (PubChem 2018a).

Sb_2S_3 is listed in community right-to-know legislation in the states of Pennsylvania and New Jersey (Sigma-Aldrich 2016).

8.2.3 Tetrazene

No regulations or standards relating to tetrazene were found. Exposure limits for tetrazene have not been established (Olin 2015).

TTZ is not listed under the right-to-know statutes in the states of California, New Jersey, Pennsylvania, Massachusetts, or Michigan. TTZ is not listed under California Proposition 65 (Olin 2015).

8.2.4 Barium nitrate

The U.S. EPA has determined a Reference Dose (RfD) for barium of 0.2 mg/kg-day based upon Benchmark Dose analysis of a 2-year drinking water study in mice. No Reference Concentration (RfC) has been established (IRIS 2005).

The U.S. EPA has established a Federal Drinking Water Standard/Guideline for barium at 2000 µg/L. State standards have been established by California (1000 µg/L), Arizona (1500 µg/L), Maine (1500 µg/L) and Minnesota (2000 µg/L) (HSDB 2006).

The OSHA Permissible Exposure Limit (PEL) for an 8-hour time-weighted average (TWA) exposure is 0.5 mg/m^3 (HSDB 2006).

The American Conference of Governmental Industrial Hygienists (ACGIH) has also established an 8-hour TWA exposure limit at 0.5 mg/m^3 (HSDB 2006).

8.2.5 Aluminum

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 2008).

The American Conference of Government Industrial Hygienists (ACGIH) has established a Threshold Limit Value (TLV) of 1 mg/m^3 for an 8-hour exposure. 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 2008).

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 1000 µg/L (HSDB 2008).

The National Institute for Occupational Safety and Health (NIOSH 2016) has established a time-weighted average (TWA) Recommended Exposure Limit (REL) of 10 mg/m^3 for total aluminum particulates, and 5 mg/m^3 for respirable particles. The OSHA Permissible Exposure Limit (PEL) is 15 mg/m^3 with 5 mg/m^3 for respirable particles (NIOSH 2016).

8.2.6 Isopropyl alcohol

The NIOSH Recommended Exposure Limit (REL) is a time-weighted 400 ppm (980 mg/m^3) with a 15-minute Short Term Exposure Limit (STEL) of 500 ppm (1225 mg/m^3). The OSHA Permissible Exposure Limit (PEL) is also a time-weighted average 400 ppm (NIOSH 2018).

The state of Connecticut has established a drinking water guideline of 2300 µg/L (PubChem 2018).

8.2.7 Methylcellulose

MC is exempt from the requirement for a tolerance when used as a thickener in accordance with good agricultural practices as an inert or active component of pesticide formulations (HSDB 2002).

8.3 Conclusions

Overall, this formulation is considered to be of low to moderate toxicity, and is certainly less toxic than the lead compounds that are being replaced. With few exceptions, the compounds involved in the formulation are generally well-understood from a toxicological perspective; specific additional testing is recommended; however, due to poor solubility and reactivity, there are limited in vitro testing options for DBX-1. Short-term animal testing may be useful for evaluating genotoxicity; however, there are potential safety issues regarding the preparation and dosing of DBX-1. In vitro followed by in vivo testing of tetrazine is recommended.

Occupational health risks appear to be low overall, but the formulation may present an ecotoxicity hazard; therefore environmental releases could represent a concern. Ecotoxicity evaluations should be considered if there is the prospect of significant environmental release.

9 Recommendations

In vitro toxicity testing is recommended for DBX-1, if feasible; testing of tetrazene is already being undertaken as part of a different requirement. Ecotoxicity testing should be considered.

10 Point of Contact

The Point of Contact for this report is Dr. William Eck, telephone 410-436-3980, DSN: 584-3980; e-mail: usarmy.apg.medcom-phc.mbx.tox-info@mail.mil.

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
DBX-1	178.59[a]	99.4[b]	284.4[b]	6.7E+04[b,c]	-1.76[b]	0.244[b]	2.41E-09[b]	8.41E-04[b]
Antimony trisulfide	339.7[c]	550[c]	1150[c]	1.75[c]	ND	ND	ND	Negligible[d]
Tetrazene	188.15[e]	100[g] (dec)	128[g] (explodes)	Insoluble in cold water; decomposes in boiling water[c]	-4.13[f]	-0.90[f]	3.58E-19[f]	7.13E-07[f]
Barium nitrate	261.35[a]	~590[h]	>590[h] (dec)	5.0E+04[i]	n/a	n/a	n/a	n/a
Aluminum	26.98[i]	660[i]	2518[i]	Insoluble[i]	n/a	n/a	n/a	n/a
IPA	60.09[c]	-89.5[c]	82.3[c]	Miscible[c]	0.05[c]	1.5[j]	8.10E-06[j]	33[c] 45.4[j]
Methyl cellulose	40,000-180,000[k]	290-305[k]	ND	Soluble in cold water (<50 ºC)[k]	ND	ND	n/a	n/a

Key:
a = Calculated from molecular formula and standard atomic weights
b = Values determined for the neutral base form of 5-nitrotetrazole
c = PubChem 2018
d = Professional judgment
e = PubChem 2015 (monohydrate form)
f = EPI Suite model prediction
g = Olin 2015
h = O'Neil 2006
i = Dean 1992
j = HSDB 2012
k = HSDB 2002

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
DBX-1	937[a]	132.5[a]	5.5[a]	Probable moderate sensitizer[a]	Possible moderate irritant[a]	Positive[a]	Indeterminate[a]
Antimony trisulfide	>2000[b]	ND	ND	Irritant[c]	Irritant[c]	ND	Negative[c]
Tetrazene	1100[a]	220.5[a]	0.626[a]	Possible irritant; probable sensitizer[a]	Possible irritant[a]	Probable[a]	Indeterminate[a]
Barium nitrate	266[d] (mouse) 355[d] (rat)	ND	ND	Irritant[e]	Irritant[e]	Negative[e]	Negative[e]
Aluminum	ND	ND	ND	Negative	Negative	ND	ND
IPA	4710-5840[f]	ND	5.3[f]	LD_{50} = 12.8 g/kg	ND	Negative[f]	Negative[f]
Methyl cellulose	ND	ND	ND	Negative[g]	Negative[g]	ND	ND

Key:
ND = No data
a = TOPKAT model estimate
b = PubChem 2018
c = HSDB 2005
d = CIDPL 2006
e = HSDB 2006
f = HSDB 2012
g = HSDB 2002

Table 5. Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
DBX-1	Mod	Low	Mod	Mod	Unk	
Antimony trisulfide	Low	Unk	Mod	Mod	Low	
Tetrazene	Mod	Mod	Mod	Mod	Unk	
Barium nitrate	Low	Low	Low	Low	Low	
Aluminum	Low	Mod	Low	Low	Low	
IPA	Low	Low	Low	Low	Low	
Methyl cellulose	Low	Low	Low	Low	Low	

Table 6. Ecotoxicity assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
DBX-1	Low	Low	Unk	Mod	Unk	
Antimony trisulfide	Unk	Unk	Unk	Low	Unk	Available information generally discourages discharge in the environment, but specific data are lacking.
Tetrazene	Low	Unk	Unk	Mod	Unk	Low
Barium nitrate	Low	Low	Low	Low	Low	
Aluminum	Low	Low	Low	Low	Unk	Moderate toxicity toward shellfish
IPA	Low	Unk	Unk	Low	Unk	
Methyl cellulose	Low	Low	Low	Low	Unk	

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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 (SDS, formerly known as Material Safety Data Sheets, MSDS). The GHS attempts to reduce differences among levels of protection for workers 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 U.N. General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While there are several aspects of the GHS, the one most important area for our purposes is classification of chemicals into various hazard categories based upon their effects and the route of exposure. Tabular extracts of the criteria for acute toxicity (both oral and inhalation), dermal, and ocular effects are included below. More information can be found in the original source (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	

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

<table>
<tr><td>Category 1
Serious Eye Damage</td><td colspan="2">Category 2
Eye Irritation</td></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><td>Acute Category I
Acute toxicity ≤ 1.00 mg/L</td><td>Acute Category II
Acute toxicity > 1.00 but ≤10.0 mg/L</td><td colspan="2">Acute Category III
Acute toxicity > 10.0 but < 100 mg/L</td></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>