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Toxicology Directorate

Toxicology Assessment for U.S. Department of Defense Strategic Environmental Research and Development Program Project WP-2400

Environmentally Sustainable Liquid Gas Generator Formulations

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Several U.S. missile and satellite systems—or their components—use hydrazine as a fuel. Hydrazine is mutagenic and is a suspected human carcinogen. Replacing this dangerous and difficult-to-handle material would improve prospects for human health and the environment, as well as reduce life cycle costs. This report assesses the known and predicted toxicological profiles of hydrazine and seven propellant components that may be used as replacements.

15. SUBJECT TERMS
hydrazine, toxicity, toxicology, hydroxylammonium nitrate, hydroxyethylhydronium nitrate, ammonium nitrate, 1-Methyl-4-amino-1,2,4-triazolium nitrate, carbohydrazide, 2-2' Bipyridyl, 1-Hydroxyethan-1,2,4-triazolium nitrate

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Commonly Used Terms

ACGIH ..... American Conference of Governmental Industrial Hygienists
APHC ..... Army Public Health Center
AR ..... Army Regulation
ATSDR ..... Agency for Toxic Substances and Disease Registry
bp ..... boiling point
CASRN ..... Chemical Abstracts Service Registry Number
CERCLA/SARA ..... Comprehensive Environmental Response, Compensation, and Liability Act/Superfund Amendments and Reauthorization Act
CFR ..... Code of Federal Regulations
DOD ..... Department of Defense
ECOSAR ..... Ecological Structure Activity Relationship
ECOTOX ..... EPA Ecotoxicology database
EC_{50} ..... median effect concentration
EPA ..... U.S. Environmental Protection Agency
ESOH ..... environmental safety and occupational health
GHS ..... Global Harmonization System
K_H ..... Henry's law constant
IC_{50} ..... half maximal inhibitory concentration
kg ..... kilogram
L ..... liter
LC_{50} ..... median lethal concentration
LD_{50} ..... median lethal (oral) dose
log K_{OC} ..... Log Organic carbon partition coefficient
log K_{OW} ..... Log Octanol-water partition coefficient
LOAEL ..... lowest-observed adverse effect level
LOEL ..... lowest observed effect level
µg ..... microgram
µL ..... microliter
µmol ..... micromolar
mg ..... milligram
mL ..... milliliter
mM ..... millimolar
MW ..... molecular weight
NOAEL ..... no-observed adverse effect level
NOEL ..... no-observed effect level
OSHA ..... Occupational Health and Safety Administration (U.S.)
ppm ..... parts per million
QSAR ..... Quantitative Structure-Activity Relationship
RDT&E ..... Research, Development, Test, and Evaluation
SDS ..... Safety Data Sheet
SERDP ..... Strategic Environmental Research and Development Program
TOX ..... Toxicology Directorate
USFDA ..... U.S. Food and Drug Administration
vp ..... vapor pressure

TOXICOLOGY REPORT NO. S.0026122-15
TOXICOLOGY ASSESSMENT FOR U.S. DEPARTMENT OF DEFENSE STRATEGIC ENVIRONMENTAL RESEARCH AND DEVELOPMENT PROGRAM PROJECT WP-2400: ENVIRONMENTALLY SUSTAINABLE LIQUID GAS GENERATOR FORMULATIONS
MARCH 2020

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 military. Safeguarding the health of Service Members, civilians, and the environment requires an assessment of alternatives before they are fielded. Residues of pyrotechnics, propellants, explosives and incendiaries that cost the Department of Defense billions of dollars and were part of mission essential activities have been found in soil, air, surface and ground water samples, creating environmental problems and interfering with training activities. 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.

1.2 Purpose

Several U.S. missile and satellite systems—or their components—use hydrazine as a fuel. Hydrazine is a colorless oily liquid that fumes in air, has a penetrating odor resembling ammonia, and is explosive in the presence of air. It is also unstable in the presence of metal ions, ultraviolet light, and is highly toxic and corrosive to skin which it readily penetrates. Hydrazine is mutagenic and is a suspected human carcinogen. Replacing this dangerous and difficult-to-handle material would improve prospects for human health and the environment, as well as reduce life cycle costs.

1.3 Conclusions

The eight substances used in formulating these propellants may be ranked generally in toxicity as:

1) Hydrazine
2) 2,2'-bipyridyl
3) Carbohydrazide
4) Hydroxylammonium nitrate [HAN]
5) Hydroxyethylhydrazinium nitrate [HEHN]
6) Ammonium nitrate [AN]
7) 1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]
8) 1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]

This ranking is based strictly on data for oral toxicity or oral toxicity predictions, but inhalation toxicity is similar in most cases. Occupational health hazards are moderate for all listed compounds, with the exception of hydrazine which has a high occupational health hazard.

Hydrazine, 2,2'-bipyridyl, and carbohydrazide are likely mutagenic in the Ames assay. Hydroxylammonium nitrate [HAN] and hydroxyethylhydrazinium nitrate [HEHN] are predicted to be developmental or reproductive toxicants.

Ecotoxicity information is generally lacking, although carbohydrazide is relatively persistent in the environment.

1.4 Recommendations

Due to the dearth of data on these substances, more in-depth experimental testing is recommended for any down-selected formulations, beginning with *in vitro* testing and progressing to *in vivo* work as indicated by circumstances.

2 REFERENCES

See Appendix A for a list of references.

3 AUTHORITY

Funding for this work was provided under Military Interdepartmental Purchase Request (MIPR) No. W74RDV41496835, dated 29 May 2014 and W74RDV70976015, dated 7 April 2017. This Toxicology Assessment addresses, in part, the environment, safety and occupational health (ESOH) requirements outlined in the following:

- DoD Directive 4715.1E, Environment, Safety, and Occupational Health (ESOH), March 19, 2005; Change 1, August 31, 2018
- Army Regulation (AR) 200–1, Environmental Protection and Enhancement, 2007
- AR 40–5, Preventive Medicine, 2007
- AR 70–1, Army Acquisition Policy, 2018

The Sponsor is the U.S. Department of Defense Strategic Environmental Research and Development Program (SERDP), Weapons Systems and Platforms program. The Principle Investigator (PI) is Dr. Nora Dimas, Aerojet Rocketdyne, Culpepper, Virginia.

4 BACKGROUND

There is currently strong international demand for a high performance, environmentally benign replacement for hydrazine in propulsion applications, especially related to spacecraft maneuver. Hydrazine fuel, typically used in such applications, comes with multiple safety concerns and added costs that could be eliminated from the life cycle costs for satellites and similar systems. Department of Defense (DoD) Missile Defense applications also have a strong interest in replacing the current toxic fuels that are used in programs like Standard Missile-3 (SM-3) and Theater/Terminal High Altitude Area Defense (THAAD) systems, both of which are part of the U.S. national missile defense system. This program seeks to develop a new, environmentally benign missile propellant formulation.

Current regulations require assessment of human health and environmental effects arising from exposure to substances in soil, surface water, and ground water. 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 or substances early in the 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 is an on-going effort, and this report represents the status of information available for this work unit as of the date of publication.

5 STATEMENT OF PROBLEM

Spacecraft and missile warhead guidance systems currently use the hypergolic fuel hydrazine for maneuvering. Hydrazine is extremely hazardous to handle, requiring personnel to be in full protective suits including self-contained breathing apparatus. Also, hydrazine fuels have a measureable shelf life, requiring that they be periodically replaced, causing additional concerns associated with disposal and potential environmental release. Users of space and missile systems are interested in developing an alternative to hydrazine that imposes fewer human and environmental health hazards, and is easier to handle during fueling and refueling operations.

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 (CASRN) (see Table 1). While all compounds do not necessarily have a single CASRN, the CASRN is an unambiguous way of accessing information for chemical substances. The CASRN 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.

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, mutagenesis, or carcinogenesis; and mode(s) and mechanisms of toxicity. Toxicological information is derived directly from primary sources whenever possible.

Sources used in this search included the U.S. National Library of Medicine's National Center for Biotechnology Information (NCBI), the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR), the EPA Ecotoxicology Database System (ECOTOX), and the Defense Technical Information Center (DTIC). Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health Organization (WHO), the International Agency for Research on Cancer (IARC) and The Merck Index (O'Neil 2006). Commercial suppliers may provide results of in-house research that do not appear in the open literature.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general categories of risk (i.e., low, moderate, or high) using criteria modified from Howe et al. (Howe et al. 2006). In addition, classification in the Globally Harmonized System (OSHA 2012) is also included for many of these compounds (See Appendix B). Table 2 describes the criteria used in the categorization, though the relative proportions of each substance were also factored into the final assessment.

If no experimental data can be located in the literature, toxicity values for the various parameters are predicted using Quantitative Structure Activity Relationship (QSAR) software where possible. Modeling packages include EPA's EPI Suite™ 4.0 (EPA 2015a), ECOSAR™ (EPA 2015b) and TOPKAT (BIOVIA 2015). EPI Suite™ and ECOSAR™ are trademarks of the EPA.

Table 1: Formulation Components

Chemical Substance	CASRN
Hydroxylammonium nitrate [HAN]	13465-08-2
Hydroxyethylhydronium nitrate [HEHN]	Unknown
Ammonium nitrate [AN]	6484-52-2
1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]	Unknown
Carbohydrazide [CBZ]	497-18-7
2-2' Bipyridyl [BP]	366-18-7
1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]	Unknown
Hydrazine	302-01-2

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 biodegradable: < 28 days	Degradation ½ life: water < 40 days, soil < 120 days	Degradation ½ life: water > 40 days, soil > 120 days
TRANSPORT	Water solubility < 10 mg/L, log K_{OC} > 2.0	Water solubility 10-1000 mg/L, log K_{OC} 2.0-1.0	Water solubility > 1000 mg/L, log K_{OC} < 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; subchronic LOAEL 5-200 mg/kg-d	Positive evidence for carcinogenicity/ mutagenicity; subchronic 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 100-10 mg/kg-d	Acute LC_{50}/LD_{50} > 0.1 mg/L or 150 mg/kg; subchronic EC_{50} > 100 µg/L or LOAEL < 10 mg/kg-d

Legend: mg/L – milligrams per liter; LOAEL – lowest-observed adverse effect level; mg/kg-d – milligrams per kilogram per day; LC_{50} – lethal concentration for 50% of the population of test animals; LD_{50} – lethal dose for 50% of the population of test animals; mg/kg – milligrams per kilogram; µg/L – micrograms per liter; EC_{50} = median effect concentration

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 K_H are typically negligible.

Table 3: Physical and Chemical Properties

Compound	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)	Aqueous solubility (mg/L) @ 25°C	log K_{ow}	log K_{oc}	Henry's Law Constant (atm-m^3/mol) @ 25°C	Vapor Pressure mmHg @ 25°C
Hydroxylammonium nitrate [HAN]	96.06[a]	nd	dec[b]	nd	nd	nd	nd	10.5 @ 0°C
Hydroxyethylhydrazinium nitrate [HEHN]	139.14[a]	-70[c]	219[c]	1E+06[c] (miscible)	-1.98[d]	-0.06[d]	1.54E-12[d]	0.023[d]
Ammonium nitrate [AN]	80.06[a]	169.6[e]	210[e] (dec)	192,000[e]	n/a	n/a	n/a	n/a
1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]	162.13[a]	nd	nd	1E+06[d]	-3.86[d]	-1.14[d]	4.43E-14[d]	0.198[d]
Carbohydrazide [CBZ]	90.086[h]	154[i] (exp)	nd	Freely soluble	-3.730[i]	-0.808[d]	6.37E-15[d]	12 @ 20°C[i]
2,2'-Bipyridyl [BP]	156.19[a]	72[j]	273.5[j]	5.93E+03[c]	1.50[j]	2.11[c]	7.09E-10[c]	1.35E-05[c]
1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]	176.15[a]	95.15[d]	288.23[d]	1E+06[d]	-4.83[d]	-2.08[d]	2.15E-18[d]	6.43E-05[d]
Hydrazine	32.05[f]	2.0[f]	113.5[f]	Miscible[f]	-2.07[g]	2[g]	6.1E-07[g]	14.4[g]

Notes: a = Calculated from molecular formula and standard atomic masses; b = dec = decomposes, (Sasse and Klein 1979); c = EPI Suite 4.11 database value; d = EPI Suite 4.11 estimate; e = (Dean 1992); f = (O'Neil 2006); g = (HSDB 2005); h = (PubChem 2018); i = (CIDPL 2013a); j = (Lide 2000)

7.2 Summaries

The summaries of the 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 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
Hydroxylammonium Nitrate [HAN]	325[a]	nd	nd	Moderate irritant[a]	Probable irritant	Negative[a]	Negative[b]
Hydroxyethyl hydrazinium nitrate [HEHN]	367[c]	19.4[b]	0.549[b]	Slight[c]	Probable irritant[b]	Positive[c]	Possible[b]
Ammonium nitrate [AN]	2217[d](rat)	nd	>88.8[a] (rat)	Irritant	Irritant	Negative	Negative
1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]	>10,000[b]	30.0[b]	>10.0[b]	Unlikely irritant or sensitizer[b]	Possible irritant[b]	Negative[b]	Indeterminate[b]
Carbohydrazide [CBZ]	311[g] (rat, ♀)	274.1[b]	1.2[b]	Irritant and sensitizer[h]	Irritant[h]	Positive[b]	Indeterminate[b]
2,2'-Bipyridyl [BP]	100[i]	60.9[c]	9.1[c]	Irritant[g]; unlikely sensitizer[c]	Irritant[c]	Positive[i]	Unlikely[c]
1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]	>10,000[b]	35.7[b]	9.0[b]	Unlikely[b]	Unlikely[b]	Possible severe irritant[b]	Indeterminate[b]
Hydrazine	59[e] (mouse), 60[a] (rat)	nd	0.746[e] (570 ppm)	LD_{50} = 91 mg/kg (rabbit); strong irritant, sensitizer[f]	Corrosive[f]	Positive	Positive

Notes: a = AFRL Operational Toxicology Branch; b = TOPKAT model estimate; c = Chemical Propulsion Information Analysis Center (CPIAC 2009); d = (HSDB 2014); e = (ACGIH 2001); f = (HSDB 2005); g = (ILO 1983) ; h = (PubChem 2018); i = (Yamaguchi 1981)

Table 5: Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Genotoxicty	Carcinogencity	Comments
Hydroxylammonium nitrate [HAN]	Mod	nd	Mod	Mod	Low	Low	
Hydroxyethyl hydrazinium nitrate [HEHN]	Mod	Mod	Mod	Mod	Mod	Mod	
Ammonium nitrate [AN]	Low	Low	Low	Low	Low	Low	Methemoglobinemia most readily expressed clinical sign.
1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]	Low	Low	Low	Low	Low	Low	Not predicted to be a developmental or reproductive toxicant
Carbohydrazide [CBZ]	Mod	Low	Mod	Mod	nd	Mod developmental/ reproductive toxicant	
2,2'-Bipyridyl [BP]	High	Low	Mod	Mod	High	Low	pKa = 4.33
1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]	Low	Low	Low	Mod	Low	Indeterminate	
Hydrazine	High	High	High	High	High	Carcinogenic to animals	

Table 6: Ecotoxicity assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
Hydroxylammonium Nitrate [HAN]	Low	Low	Mod	Mod	nd	
Hydroxyethyl hydrazinium nitrate [HEHN]	Low	nd	nd	Mod	nd	
Ammonium nitrate [AN]	Low	Low	Low	Low	Low	Amphibians most sensitive
1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]	Low	nd	nd	Low	nd	
Carbohydrazide [CBZ]	Low	nd	nd	Mod	nd	
2,2'-Bipyridyl [BP]	Low	nd	nd	High	nd	Some data on aquatic and terrestrial plants, but data are uninterpretable.
1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]	Low	nd	nd	Low	nd	
Hydrazine	High	High	Mod	High	nd	

7.3 Hydroxylammonium nitrate [HAN]

7.3.1 General Information

Hydroxylammonium nitrate [HAN] is the nitrate salt of hydroxylamine (Figure 1).

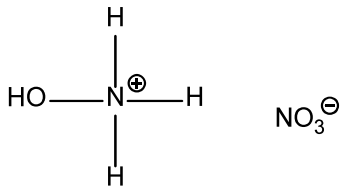

Figure 1: Hydroxylammonium nitrate [HAN]

7.3.2 Toxicology Data

Data gaps for HAN cannot be filled by TOPKAT modeling because the molecule contains no carbon atoms. Due to the similarity between HAN and hydroxylamine (HA), it is reasonable to assume that the mechanism of action is similar between the two compounds. HA, and presumably HAN, rapidly induces methemoglobin formation as well as depletion of glutathione levels. It is believed HA causes damage to blood via two separate mechanisms—production of free radicals and inhibition of the enzymes glutathione S-transferase (GST) and NADPH methemoglobin reductase (NADPH-HbR). Following HA-exposure, blood cell cytotoxicity is observable in the formation of Heinz bodies and increased lipid peroxidation. HA is a potent inhibitor of platelet aggregation and riboflavin availability is also decreased. Additionally, brain levels of GABA (γ- aminobutyric acid) are observed, followed by paralysis and cessation of breathing (Evelo et al. 1998).

7.3.2.1 Oral

The oral lethal dose in humans is estimated to be between 50 and 500 mg/kg. In animals, a fatal overdose causes seizures, paralysis of the respiratory muscles, and death. Sublethal signs and symptoms of exposure include headache, vertigo, restlessness, tinnitus, dyspnea, nausea, vomiting, proteinuria, hematuria, anemia, leukocytosis, platelet aggregation, jaundice, and

splenomegaly. Ingestion of hydroxylamine also causes methemoglobinemia and depletion of glutathione, indicating production of reactive oxygen species (HSDB 2003).

7.3.2.2 Inhalation

The neutral surrogate compound hydroxylamine (HA) is highly irritating to mucous membranes. Due to its salt nature, and presumed lack of volatility, HAN is likely to only be present in particulate form for inhalation, but will have the same effects as HA. Ingestion of HA leads to rapid, significant methemoglobinemia and depletion of glutathione. HA has also caused dose-related hypotension in test animals (HSDB 2003).

7.3.2.3 Dermal

HA and its salts are corrosive to skin. Repeated exposure may enhance allergic reaction, particularly of hands and forearms beginning 1-2 weeks to 2-5 years after initial exposure. Cases of eczema may be observed after prolonged contact (HSDB 2003).

7.3.2.4 Ocular

HA and its salts are highly irritating to eyes and mucous membranes. Nystagmus has been observed in test animals; a yellow-brown deposit on the conjunctiva and cornea are possible (HSDB 2003).

7.3.2.5 Developmental and Reproductive

Malformations have been observed in rabbits following exposure to HA (HSDB 2003). DeSesso (DeSesso et al. 2000) observed cellular debris, an indicator of cell death, in limb buds of gestation day 12 rabbit embryos 4 hours after injection of hydroxylamine hydrochloride and various other related compounds via either intracoelomic (2.66 µmol/embryo) or subcutaneous (8.55 mmol/kg) injection. Early cell death was not observed. The authors concluded the data were consistent with a free radical mechanism involving the terminal hydroxylamine group.

7.3.2.6 Neurotoxicity

Hydroxylamine elevates brain GABA levels in rats; systemic poisoning is characterized by cyanosis, convulsions, and coma (HSDB 2003).

7.3.2.7 Genotoxicity

HA has been observed to cause point mutations in DNA replication (Chatake et al. 1999). HA is negative in *in vitro* leukocyte and lymphocyte tests (HSDB 2003).

7.3.2.8 Carcinogenicity

HA is not listed as a human carcinogen (HSDB 2003). Although HA is a potent mutagen *in vitro*, it has not been shown to possess carcinogenic capabilities, and has shown carcinostatic activity against certain tumors in animals (Gross 1985).

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

If released to air, HAN will exist solely in particulate form due to its salt nature. Airborne HAN will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals. The half-life for this reaction is estimated to be 18 hours (HSDB 2003).

If released to water, HAN is likely to be highly mobile, and may pose a hazard to ground, surface, and drinking water (HSDB 2003).

If released to soil, HAN is expected to have high mobility, based upon an estimated K_{OC} of 14. The pKa of HA is 5.94, indicating HA and HAN will exist as both ionic and protonated species in the environment, and exhibit the same fate and transport characteristics. Volatilization from moist soil surfaces is not expected to be an important fate process for HAN; based upon an estimated Henry's Law Constant of 6.9 x 10-9 atm-m3/mol for HA, the protonated form will not volatilize (HSDB 2003).

An estimated bioconcentration factor (BCF) of 3 suggests the potential for bioconcentration in aquatic organism is low (HSDB 2003).

7.3.2.9.2 Ecotoxicity

HA-HCl treatment of wheat seed induced chromosome aberrations in mitotic and meiotic cells of resulting plants. Frequency of chromosomal aberration was 2-3 fold high than for seed soaked in distilled water (HSDB 2003).

EPA's ECOSAR program models HA as a neutral organic, and estimates a 96-hour EC_{50} in green algae of 1970 mg/L, a 48-hour LC_{50} in Daphnia of 9073 mg/L, and a 96-hour LC_{50} in fish of 21,530 mg/L. Since these values are based upon general narcosis, experimental values would likely be lower.

7.3.2.9.3 Degradation/Treatment

Abiotic photodegradation of HA by photochemically produced peroxy radicals is an important environmental fate in surface waters, with a half-life of about 2 hours (HSDB 2003).

EPA's EPI Suites program predicts HA, and therefore HAN, will be poorly removed (< 2%) by standard wastewater treatment plants.

7.4 Hydroxyethylhydrazinium nitrate [HEHN]

7.4.1 General Information

HEHN is a component of a proposed monopropellant, AF-M315E. The new formulation is designed to have less vapor toxicity than hydrazine, but greatly improved volumetric and specific impulse (see Figure 2).

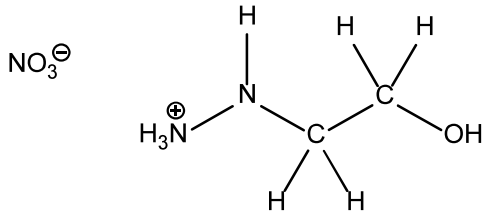

Figure 2: Hydroxyethylhydrazinium nitrate [HEHN]

7.4.2 Toxicology Data

7.4.2.1 Oral

The Air Force Research Lab determined the oral LD_{50} of HEHN in rats to be 367 mg/kg (CPIAC 2009). The TOPKAT model prediction for the neutral compound is very similar, at 283.1 mg/kg. The chronic LOAEL is predicted by TOPKAT to be 19.4 mg/kg-day.

7.4.2.2 Inhalation

No experimental data were found. TOPKAT modeling predicts the median inhalation toxicity (LC_{50}) in rats to be 0.549 g/m^3-hour.

7.4.2.3 Dermal

HEHN was found to be a slight dermal irritant (CPIAC 2009). TOPKAT modeling predicts HEHN will not be a skin sensitizer.

7.4.2.4 Ocular

No experimental data were found. TOPKAT modeling predicts HEHN is probably an ocular irritant.

7.4.2.5 Developmental and Reproductive

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

7.4.2.6 Neurotoxicity

No experimental data were found.

7.4.2.7 Genotoxicity

HEHN is reported to be positive in the Ames mutagenicity assay, but the available information does not indicate whether this was with or without microsomal activation (AFRL 2002).

7.4.2.8 Carcinogenicity

No experimental data were found. TOPKAT modeling of HEHN suggests only a moderate likelihood of carcinogenicity. The reference compound, hydrazine, is categorized as a possible human carcinogen, which correlates well with the modeling prediction.

7.4.2.9 Ecotoxicology

7.4.2.9.1 Fate and Transport

HEHN has a high aqueous solubility and low log K_{OC}, making transport in ground water a significant hazard. Partition to the atmosphere from water or wet surfaces is highly unlikely, as is vaporization from dry surfaces, due to the salt-nature of HEHN. EPA's EPI Suite predicts a log BCF of 0.50, indicating no tendency to bioaccumulate.

7.4.2.9.2 Ecotoxicity

No experimental data were found. For the neutral compound, TOPKAT predicts an EC_{50} in Daphnia of 93.3 mg/L at moderate confidence, and an LD_{50} in fish of 15.0 mg/L at low confidence.

EPA's ECOSAR program models HEHN as a hydrazine, and predicts a 96-hour EC_{50} in green algae of 3.52 mg/L, a 48-hour LC_{50} in Daphnia of 231.8 mg/L, and a 96-hour LC_{50} in fish of 19.46 mg/L.

7.4.2.9.3 Degradation/Treatment

No experimental data were found. EPI Suite modeling predicts HEHN will not be readily biodegradable, with environmental persistence of days to weeks. However, biodegradation occurs rapidly under anaerobic conditions.

HEHN is predicted to be poorly removed (< 2%) by standard waste water treatment plants, with most of the removal being accomplished via sludge adsorption.

7.5 Ammonium nitrate [AN]

7.5.1 General Information

Ammonium nitrate is a common, simple inorganic compound formed from the condensation of hydrochloric acid and ammonia (see Figure 3). Physically, it forms white, orthorhombic crystals. The dry solid is hygroscopic. Its most common use is as a fertilizer, but when mixed with an organic fuel can be used to make field-expedient explosives of significant power. A truck containing an ammonium nitrate-fuel oil mixture was used to devastate the Murrah Federal Office building in Oklahoma City, Oklahoma in 1995. Ammonium nitrate is also used in medical icepack replacements, as the heat of solution is strongly endothermic, producing a cold pack "on demand" (HSDB 2014). As with other nitrate salts, consumption may produce methemoglobinemia due to oxidation of the Fe^{2+} ion.

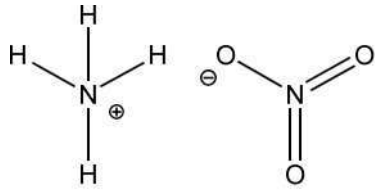

Figure 3: Ammonium nitrate [AN]

7.5.2 Toxicology Data

Workers producing AN have occupational contact with the substance in both the aerosol and gaseous (ammonia) forms. Illnesses of the respiratory apparatus and musculoskeletal system predominate in the morbidity structure. Clinical examination of workers in the production of AN shows frequent cases of chronic bronchitis and radiculoneuropathy. Function studies show damage to the airways, myocardiodystrophy, and changes in electroencephalogram (EEG) T-waves (Tsimakuridze et al. 2005).

7.5.2.1 Oral

According to the European Commission EUCLID dataset, the oral LD_{50} in rats is reported to be 2217 mg/kg or 2800 mg/kg (HSDB 2014).

A single oral dose of 2 g/kg to sheep caused death 12 hours to 17 days after administration (HSDB 2014).

7.5.2.2 Inhalation

According to the European Commission EUCLID dataset, the LC_{50} for a 4-hour inhalation in rats is > 88.8 mg/L (HSDB 2014).

Inhalation is irritating to mucous membranes of the respiratory tract, causes severe lung congestion, coughing, difficulty breathing, and acid urine. Inhalation of large amounts of AN also causes system acidosis and abnormal hemoglobin (HSDB 2014).

Twenty normal and 19 asthmatic human subjects were exposed for 2 hours to an ammonium nitrate aerosol at concentrations of 200 µg/m^3 with intermittent exercise and heat stress. Neither the normal nor asthmatic subjects showed significant differences in their lung function tests or symptom scores, nor did other significant symptoms occur (Kleinman et al. 1980).

Sprague-Dawley rats were exposed to 1 mg/m^3 ammonium nitrate 6 hours/day, 5 days/week for 4 weeks. The exposure had no effect on body weights, lung volume, vital capacity, or histologic structure of ciliated epithelial cells of the respiratory tract (HSDB 2014).

7.5.2.3 Dermal

A clinical case of contact dermatitis was reported in a farmer after sowing sorghum and wheat using urea and calcium-ammonium nitrate (CAN) fertilizers (Pasricha and Gupta 1983). Patch tests revealed that the CAN fertilizer was the source of the sensitivity.

AN was found to be moderately irritating in rabbits by the Draize test. The mean erythema and edema scores were calculated to be 0.1 and 0, respectively following a simple 4-hour application. No erythema was observed in any animals 48 or 72 hours following decontamination. Repeated (x5) applications of 500 mg of test sample to each rabbit caused only very slight edema in two of the rabbits and slight erythema in the third (HSDB 2014).

7.5.2.4 Ocular

Ammonium nitrate is an eye irritant (HSDB 2014).

7.5.2.5 Developmental and Reproductive

A mixture designed to mimic agricultural run-off consisting of five pesticides and ammonium nitrate fertilizer, per survey data from California (pesticides) and Iowa (fertilizer), was administered in drinking water to Sprague-Dawley rats on gestation days (GD) 6 to 20 at 3 dose levels: 1X, 10X and 100X median concentration in the environment. Dams were monitored daily for signs of toxicity, and fetuses were removed on GD 20 for evaluation. Maternal body weights, food and water consumption, and clinical signs were all similar to control values. No adverse effects were observed for measures of embryo/fetal toxicity, including resorptions per litter, live litter size, and fetal body weight. The mixture did not cause an increased incidence of malformations or variations (Heindel et al. 1992).

In an experiment parallel to the one in the preceding paragraph, but conducted in mice, Swiss mice were dosed at 1X, 10X and 100X median concentration in the environment for a period of 18 weeks (George et al. 1993). F0 mice were fertile throughout the exposure, and the mixture did not affect reproductive competence, F0 body weight, food or water consumption, organ weights, or sperm parameters at necropsy. No treatment-related clinical signs were noted. F1 pre-weaning growth and maturation were unaffected, and no treatment-related clinical signs or adverse effects on F1 reproductive competence, food and water consumption, male or female body weight, or selected male and female organ weights, sperm parameters, vaginal cytology, or histology of selected organs.

7.5.2.6 Neurotoxicity

No experimental data were found.

7.5.2.7 Genotoxicity

Ammonium nitrate at 5 mg/plate was negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 with or without metabolic activation (HSDB 2014).

7.5.2.8 Carcinogenicity

Nitrates can be transformed to nitrites by certain microorganisms in the soil and in the mouth and stomach. This transformation is followed by nitrosation of secondary amines and amides in the diet. The resulting nitrosamines are mutagenic, but humans are naturally exposed to the precursors as a part of a normal diet. The average Western diet contains 1-2 mmol nitrate/person/day (Hotchkiss 1992).

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

7.5.2.9 Ecotoxicology

7.5.2.9.1 Fate and Transport

Ammonium nitrate is readily soluble in water and will be solubilized when water is present. However, both the cation and anion are essential nutrients for plants, and therefore will be readily removed from soil when plants are present. Small discharges to surface water are also expected to be taken up by plants, but larger discharges can result in toxicity to aquatic species or to ecological upset due to rapid plant (algae) growth and subsequent death. Nitrates can also be metabolized by bacteria, especially in anaerobic environments (HSDB 2014).

7.5.2.9.2 Ecotoxicity

Influence of ammonium nitrate on embryonic and larval stages of anuran amphibians (i.e. frogs, toads and tree frogs) has been studied. Significant differences were observed in sensitivity to ammonium nitrate as a function of developmental stage in Iberian painted frog (*Discoglossus galgano*), Western spadefoot toad (*Pelobates cultripes*), and Natterjack toads (*Bufo calamita*). In *D. galganoi* and *P. cultripes* younger individuals displayed greater acute effects than older individuals. All (100%) of the *P. cultripes* hatchlings died after 4 days of exposure to a nominal concentration of 225.8 mg nitrogen (as ammonium nitrate)/L, where fewer than 40% of individuals from older larval stages died when exposed to this concentration. *B. calamita* showed a higher sensitivity in later larval stages after 12 days of exposure (Ortiz et al. 2004).

The minimum lethal toxicity of ammonium nitrate for *Rana temporaria chensinensis* tadpoles was 0.91 g/L, and the maximum tolerance concentration was 0.83 g/L. In field experiments, ammonium nitrate concentrations of 0.25 g/L had no adverse effects on the tadpoles, as reflected by their growth rates (Oldham et al. 1997; HSDB 2014).

In the Pacific tree frog (*Pseudacris regilla*), the 4-day LC_{50} was 135.4 mg/L, and decreased to 55.2 mg/L for a 10-day exposure. The comparable values in the common laboratory African clawed toad (*Xenopus laevis*) were 100.7 mg/L for a 4-day exposure and 52.9 mg/L for a 10-day

exposure. The LOAEL for ammonium nitrate was calculated at 24.6 mg/L in *P. regilla*, and 99.5 mg/L for *X. laevis* (Schuytema and Nebeker 1999).

In the common toad (*Bufo bufo*), ammonium nitrate LC_{50} of 2199 mg/L and 2112 mg/L for 96-hour and 168-hour exposures, respectively, were determined. The exposure of tadpoles to nominal concentrations of 100 mg/L ammonium nitrate (measured as nitrate) for 24-, 48-, or 72-hours caused a significant decrease in tadpole activity, but no clear reduction in food consumption or delay of development (Xu and Oldham 1997).

Rana catesbiana egg masses were exposed to 0, 5, or 10 mg nitrate/L for seven days (Puglis and Boone 2007). Ammonium nitrate was found to have no effect on hatching and survival of tadpoles at these concentrations.

Ruminants may develop methemoglobinemia by consumption of quantities of nitrate. This is due to the reducing environment of the rumen, resulting in rapid conversion of nitrates to the more toxic nitrites. Clinical signs may be non-specific, but in cattle often involve decreased weight gain and food efficiency, decreased milk production, poor reproductive capacity, and impaired health of epithelial tissues as expressed by digestive tract and respiratory disorders (HSDB 2014).

An EC_{50} for a 24-hour exposure to Daphnia was reported to be 555 mg/L (HSDB 2014).

LC_{50} for ammonium nitrate in Rainbow trout (*Oncorhynchus mykiss*) for a 96-hour exposure is 6000 mg/L, and 74 mg/L in Common carp (*Cyrinus carpio*) for a 48-hour exposure (HSDB 2014).

Effect of ammonium nitrate contaminated soil on snapping turtle (*Chelydra serpentina*) egg survivorship was evaluated (deSolla and Martin 2007). Eggs were incubated in garden soil that had received ammonium nitrate at rates up to 2000 kg/ha in 2005. In the field, the ammonium nitrate was observed to have no impact on hatching success or development of the young turtles, despite overt toxicity to endogenous plants. In the lab, hatching success was reduced, body mass of young was less, and there was reduced post-hatch survival compared to controls. The difference in outcome between the lab and field exposures is probably attributable to reduction in fertilizer concentration via soil leaching and atmospheric loss (of ammonia).

One study found that ammonium nitrate negatively impacted egg-laying by the snail *Biomphalaria alexandrina* more than phosphorous- or sulfur-containing fertilizers (Abdel-Hamid et al. 1997).

Larvae of the newt *Lissotriton vulgaris* were exposed to ammonium nitrate at 0, 100, 200, or 500 mg/L in artificial pond water. Larvae exposed at 200 or 500 mg/L for periods of 24, 48, or 72 hours were significantly smaller than controls at metamorphosis, however survival was high (HSDB 2014).

A study collected wild, gravid females of Carbonell wall lizards (*Podarcis carbonelli*) and Spanish wall lizards (*Podarcis hispanica*) from areas in which they were abundant (Marco et al. 2004). Eggs were obtained within 15 days of the females being captured. Eggs were exposed to

one of 4 distinct environments: 1) plants (to absorb some of the ammonium nitrate fertilizer) and fertilizer, 2) plants and control, 3) no plants and fertilizer, and 4) no plants and control. Ammonium nitrate was initially applied at a rate equal to 100 mg/L of soil; eggs were exposed to treatment for an average of 50 days. Mortality was only observed for eggs exposed to fertilizer in the absence of plants (treatment 3), where 27% of the eggs died. Hatchlings from eggs incubated with fertilizer were significantly smaller in length and mass; effects that were not mitigated by the presence of plants. A test of hatchling running speed indicated no differences among any of the treatment groups over a distance of 100 cm.

7.5.2.9.3 Degradation/Treatment

Ammonium nitrate is readily taken up by both terrestrial and aquatic plants as an essential nutrient. It will also be consumed by bacteria (HSDB 2014).

7.6 1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]

7.6.1 General Information

AMTN is under evaluation as a component for a monopropellant formulation to replace hydrazine (see Figure 4).

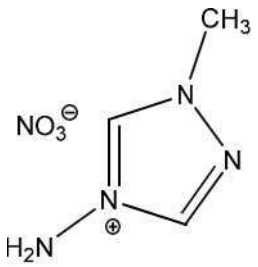

Figure 4: 1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]

7.6.2 Toxicology Data

No experimental data were found. All information below is based upon QSAR analysis using TOPKAT (BIOVIA 2015), EPI Suite 4.11 (EPA 2015a), and ECOSAR (EPA 2015b).

7.6.2.1 Oral

TOPKAT modeling predicts an oral LD_{50} in rats of >10,000 mg/kg at high confidence; the chronic LOAEL is predicted to be 30.0 mg/kg-day at low confidence. Based upon the acute toxicity prediction, AMTN is essentially non-toxic.

7.6.2.2 Inhalation

TOPKAT modeling predicts an inhalation LC_{50} in rats of >10 g/m^3-hour at high confidence, making AMTN non-toxic via inhalation.

7.6.2.3 Dermal

TOPKAT modeling predicts AMTN is unlikely to be either a dermal irritant or sensitizer at moderate confidence.

7.6.2.4 Ocular

TOPKAT modeling predicts AMTN is possibly an ocular irritant at moderate confidence.

7.6.2.5 Developmental and Reproductive

TOPKAT modeling predicts AMTN will not be a developmental or reproductive toxicant at moderate confidence.

7.6.2.6 Neurotoxicity

No experimental data were found.

7.6.2.7 Genotoxicity

TOPKAT modeling predicts AMTN will not be mutagenic in the Ames mutagenicity test at high confidence.

7.6.2.8 Carcinogenicity

TOPKAT modeling of AMTN for carcinogenicity is indeterminate.

7.6.2.9 Ecotoxicology

7.6.2.9.1 Fate and Transport

Based upon a high predicted solubility and a predicted log K_{OC} of -1.14, AMTN is expected to be readily transported in groundwater and will probably pose a hazard to surface and drinking water. Based upon a predicted Henry's Law constant of 4.43 x 10-14 atm-m^3/mol, AMTN is not expected to partition to the atmosphere from water or wet surfaces. AMTN will exist in the atmosphere only in particulate form. The salt nature of the compound also makes it unlikely to vaporize from dry surfaces. Bioaccumulation in aquatic species is expected to be negligible based upon a predicted log K_{OW} of -3.86.

7.6.2.9.2 Ecotoxicity

No experimental data were found. TOPKAT modeling predicts an EC_{50} in Daphnia of 3800 mg/L at low confidence. A prediction could not be made for fathead minnow due to lack of a suitable model.

EPA's ECOSAR program models AMTN as a non-fused triazole, and predicts a 96-hour EC_{50} in green algae of 5585 mg/L, a 48-hour LC_{50} in Daphnia of 1325 mg/L, and an LC_{50} in fish of 1.8 x 106 mg/L, which may be greater than the compound's solubility (i.e., no effect at saturation).

7.6.2.9.3 Degradation/Treatment

AMTN is expected to be moderately persistent in the environment with persistence of days to weeks. The half-time for AMTN degradation by hydroxyl radicals in the atmosphere is predicted to be 12.5 hours.

AMTN is predicted to be poorly removed (< 2%) by physical processes at wastewater treatment plants.

7.7 Carbohydrazide [CBZ]

7.7.1 General Information

Carbohydrazide (CBZ) is a white crystalline solid (see Figure 5) (Sigma-Aldrich 2020). Synonyms include 1,3- diaminourea, carbonic dihydrazide, carbonohydrazide, and 4-amino-semicarbazide, as well as several others. Industrial uses include in corrosion inhibitors, anti-scaling agents, fuels, additives, and lubricants (PubChem 2020b) and in water desalinization plants in place of hydrazine (Rahman et al. 2018).

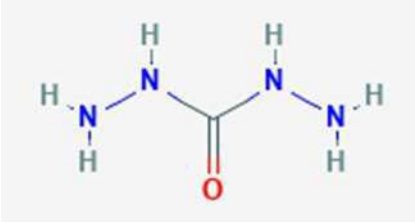

Figure 5: Carbohydrazide [CBZ]

7.7.2 Toxicology Data

CBZ decomposes to produce hydrazine (Rahman et al. 2018).

7.7.2.1 Oral

The oral LD_{50} in female rats is reported to be 311 mg/kg; this corresponds to classification in the GHS of Category 4 (Sigma-Aldrich 2020). TOPKAT modeling predicts a chronic LOAEL of 274.1 mg/kg-day.

7.7.2.2 Inhalation

CBZ is reported to cause respiratory tract irritation (PubChem 2020b). TOPKAT modeling predicts an inhalation LC_{50} in rats of 1.2 g/m^3-hour.

7.7.2.3 Dermal

CBZ is both a skin irritant and sensitizer (Sigma-Aldrich 2020).

7.7.2.4 Ocular

CBZ is a serious eye irritant (PubChem 2020b).

7.7.2.5 Developmental and Reproductive

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

7.7.2.6 Neurotoxicity

Methyldithiocarbazinate, a sulfur analog of carbohydrazide, has been noted to cause convulsions in laboratory animals. In whole brain homogenates from mice sacrificed at the onset of seizures, activity of the enzyme glutamide decarboxylase was significantly reduced. Pretreatment of the animals with pyridoxal phosphate conferred protection against seizures and death (Meldrum et al. 1975).

7.7.2.7 Genotoxicity

No experimental data were found. TOPKAT modeling predicts CBZ will be mutagenic in the Ames assay.

7.7.2.8 Carcinogenicity

No experimental data were found. TOPKAT modeling is indeterminate.

7.7.2.9 Ecotoxicology

7.7.2.9.1 Fate and Transport

As CBZ is freely soluble in water, it will be highly mobile in groundwater, and will likely pose a hazard to surface and drinking water. CBZ will not partition to the atmosphere from water or wet surfaces. CBZ will exist in the atmosphere only in particulate form. CBZ is not expected to bioaccumulate in aquatic organisms.

7.7.2.9.2 Ecotoxicity

A manufacturer's SDS classifies CBZ in GHS Category 2 for both acute and chronic aquatic toxicity (Sigma-Aldrich 2020).

The 72-hour EC_{50} for green algae is reported to be 9.5 mg/L, the 48-hour LC_{50} for Daphnia is 96 mg/L, and the 96-hour LC_{50} in Bluegill (*Lepomis macrochirus*) is 190.0 mg/L (Sigma-Aldrich 2020).

7.7.2.9.3 Degradation/Treatment

EPA's EPI Suite predicts CBZ will not readily degrade in the environment, with persistence in the environment of days to weeks.

EPA's EPI Suite also predicts CBZ will be poorly removed by wastewater treatment plants (< 2%), primarily by sludge adsorption.

7.8 2,2'-Bipyridyl [BP]

7.8.1 General Information

BP is a white, crystalline solid at room temperature (see Figure 6). It is used as a chemical intermediate for the production of the herbicide diquat, as an indicator for photometric determination of silver, cadmium, copper, iron, and molybdenum, and as an iron chelating agent. Synonyms for this compound include α,α'-bipyridyl, α,α'- bipyridine, bipyridine, 2,2'-bipridin, α,α'-dipyridine, and 2-(2-pyridyl)pyridine.

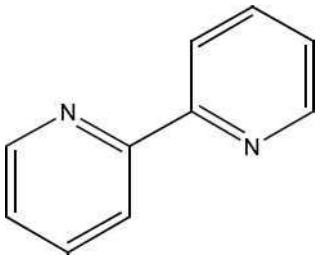

Figure 6: 2,2'-Bipyridyl [BP]

7.8.2 Toxicology Data

7.8.2.1 Oral

The oral LD_{50} in rats is reported to be 100 mg/kg (PubChem 2020a). TOPKAT modeling predicts chronic LOAEL of 60.9 mg/kg-day at high confidence.

BP administered to rats either orally or intraperitoneally in doses of 50, 100, or 250 mg/kg caused tremors and slight ptosis which completely disappeared in 24 hours (Taylor et al. 1969). Under similar circumstances, BP was noted to decrease the level of norepinephrine and inhibited dopamine β-hyrdroxylase activity in the brain in a dose-dependent manner. However, dopamine and hydroxytryptamine levels were not affected, and observed tremors, hypothermia, and hypotension from administration of BP did not appear to be related to depletion of norepinephrine (PubChem 2020a).

7.8.2.2 Inhalation

TOPKAT modeling predicts an inhalation LC_{50} in rats of 9.1 g/m^3-hour at high confidence.

Pyridine and its derivatives cause local irritation on contact with the skin, mucous membranes, and cornea (PubChem 2020a).

7.8.2.3 Dermal

The dermal LD_{50} for BP is reported to be 938 mg/kg in the rat (Sigma-Aldrich 2015).

Pyridine and its derivatives cause local irritation on contact with the skin, mucous membranes, and cornea (PubChem 2020a). TOPKAT modeling predicts BP is unlikely to be a dermal sensitizer.

7.8.2.4 Ocular

Pyridine and its derivatives cause local irritation on contact with the skin, mucous membranes, and cornea (PubChem 2020a).

An SDS for the compound indicates BP produces mild irritation (Sigma-Aldrich 2015).

7.8.2.5 Developmental and Reproductive

Data in the TOPKAT database indicates BP is a recognized developmental toxicant.

Rats treated with 0.5% solutions of BP (1-2 mL/kg-day) had alterations of testicular parenchyma involving both cells of the seminal epithelium and to a lesser extent those of the interstitial tissue. Effects were more marked in the peripheral tubules (Palmieri et al. 1978).

7.8.2.6 Neurotoxicity

No experimental data were found.

7.8.2.7 Genotoxicity

BP is reported to be mutagenic in the Ames test (PubChem 2020a).

7.8.2.8 Carcinogenicity

No experimental data were found. TOPKAT modeling predicts BP is not likely to be carcinogenic.

7.8.2.9 Ecotoxicology

7.8.2.9.1 Fate and Transport

With an estimated water solubility of nearly 6000 mg/L and log K_{OW} of 2.11, BP is expected to have a moderate ability to migrate in groundwater, possibly posing a hazard to surface and drinking water. BP is expected to not readily evaporate from water or wet surfaces based upon its Henry's Law Constant, and will exist in the atmosphere as a vapor-particulate mix. BP will be

removed from the atmosphere by both wet and dry deposition. Vapor-phase BP will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals, with an estimated half-life of 12.5 days. BP is not predicted to bioaccumulate.

7.8.2.9.2 Ecotoxicity

BP is a strong inhibitor of *Entamoeba histolytica*, a causative agent of amebiasis (PubChem 2020a).

TOPKAT modeling predicts an EC_{50} in Daphnia of 5.5 mg/L at high confidence, and an LC_{50} in fathead minnow of 1.7 mg/L at moderate confidence.

EPA's ECOSAR program predicts a 96-hour EC_{50} in green algae of 145.8 mg/L, a 48-hour LC_{50} in Daphnia of 247.98 mg/L, and a 96-hour LC_{50} in fish of 462.4 mg/L.

7.8.2.9.3 Degradation/Treatment

EPA's EPI Suite predicts BP will not readily degrade in the environment, with persistence in the environment of weeks to months.

EPA's EPI Suite also predicts BP will be poorly removed by wastewater treatment plants (< 2%), primarily by sludge adsorption.

7.9 1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]

7.9.1 General Information

HEATN is a component of a proposed propellant, AFRL 824S (see Figure 7).

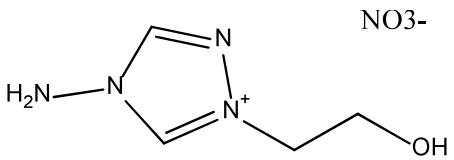

Figure 7: 1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]

7.9.2 Toxicology Data

No experimental data were found. All values below are based upon QSAR analysis.

7.9.2.1 Oral

TOPKAT modeling predicts an oral LD_{50} in rats of > 10 g/kg. The chronic LOAEL is predicted to be 35.7 mg/kg. This toxicity value exceeds the classification limits of the GHS.

7.9.2.2 Inhalation

TOPKAT modeling predicts an inhalation LC_{50} in rats of 9.0 g/m^3-hour. This toxicity value exceeds the classification limits of the GHS.

7.9.2.3 Dermal

TOPKAT modeling predicts HEATN is an unlikely irritant or sensitizer.

7.9.2.4 Ocular

TOPKAT modeling predicts HEATN is possibly a severe ocular irritant.

7.9.2.5 Developmental and Reproductive

TOPKAT modeling predicts HEATN is not a developmental or reproductive toxicant at moderate confidence.

7.9.2.6 Neurotoxicity

No experimental data were found.

7.9.2.7 Genotoxicity

TOPKAT modeling predicts HEATN will not be mutagenic in the Ames assay.

7.9.2.8 Carcinogenicity

TOPKAT modeling is indeterminate, but HEATN is not likely to be carcinogenic based upon the genotoxicity prediction.

7.9.2.9 Ecotoxicology

7.9.2.9.1 Fate and Transport

HEATN is predicted to be very water soluble. The log K_{OC} suggests it will not bind to soil. It is expected to be highly mobile in groundwater and will likely pose a hazard to surface and drinking water. Volatilization from water or wet surfaces is not anticipated due to the small value of the Henry's Law constant. Volatilization is expected to occur from dry surfaces, and HEATN will exist in the atmosphere primarily as a vapor. Bioconcentration in aquatic species is not anticipated.

7.9.2.9.2 Ecotoxicity

EPA's ECOSAR program predicts a 96-hour EC_{50} in green algae of 345 mg/L, a 48-hour LC_{50} in Daphnia of 5.8 x 10^3 mg/L, and a 96-hour LC_{50} in fish of 4.65 x 10^4 mg/L. These toxicity values exceed the classification limits of the GHS (UNECE 2015).

7.9.2.9.3 Degradation/Treatment

HEATN is predicted to biodegrade in the environment with a half-life of days to weeks. It is predicted to rapidly oxidize in the atmosphere.

HEATN is expected to be poorly removed (< 2%) by physical wastewater treatment processes.

7.10 Hydrazine

7.10.1 General Information

Hydrazine is a colorless oily liquid that fumes in air with an ammonia-like odor (see Figure 8). It is used as a propellant in liquid-fuel missiles. It has a penetrating odor resembling ammonia, and burns with a violet flame. Hydrazine will explode during distillation if air is present, and is also affected by UV light and metal ion catalysts. It can be stored for years if sealed in glass and protected from light (O'Neil 2006). There is a relatively large amount of data available on hydrazine, particularly in laboratory animals. The examples cited below represent only a portion of the available information, but should be considered representative.

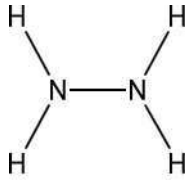

Figure 8: Hydrazine

7.10.2 Toxicology Data

Toxic effects of hydrazine include conjunctivitis, pulmonary edema, hemolytic anemia, ataxia, convulsions, and kidney and liver toxicity (HSDB 2005).

7.10.2.1 Oral

Oral toxicity values for hydrazine are reported to be 59 mg/kg in the mouse and 60 mg/kg in the rat (CIDPL 2013b). In cases of acute human poisoning, hydrazine may induce vomiting, severe irritation of the respiratory tract with development of pulmonary edema, central nervous system depression, and hepatic and renal damage (HSDB 2005).

Golden hamsters administered daily doses of 0.74 or 0.68 mg hydrazine over a 15-20 week period developed liver lesions, reticuloendothelial cell proliferation, cirrhosis, bile-duct proliferation, and degenerative fibrous cells in hyalinized tissues (Sheftel 2000).

Administration of hydrazine to mice, rats, and hamsters was found to result in rapid methylation of liver DNA guanine for which endogenous formaldehyde appeared to be the source of the methyl moiety. Hamsters were given hydrazine sulfate at 170, 340, and 510 mg/L in drinking water for 2 years, during which levels of methylation of DNA guanine in liver, kidney, and lung

was observed. Hepatocellular carcinomas were observed in hamsters treated with the highest doses of hydrazine sulfate after 78 weeks of exposure; the incidence of liver cancer was dose-related over the course of the experiment (Bosan et al. 1987).

7.10.2.2 Inhalation

The LC_{50} for inhalation of hydrazine in rats is reported to be 570 ppm (CIDPL 2013b).

Groups of dogs, monkeys, rats, and mice were exposed to either 1 or 6.2 ppm hydrazine for 24 hours/day, 7 days/week, or 1 or 5 ppm hydrazine for 6 hours/day, 5 days/week for 6 months. Mortality was seen in mice and dogs, but not in monkeys or rats. Dogs showed hematologic deficits and increased numbers of reticulocytes. Liver changes that consisted of moderate to severe fatty infiltration were marked in mice and dogs, were slight to moderate in monkeys, and were absent in rats (HSDB 2005).

Ninety-seven percent pure hydrazine vapor was administered to mice, rats, Syrian golden hamsters, and beagles at exposure concentrations of up to 1.0 ppm for C57BL/6 mice and dogs, and 5.0 ppm for F344 rats and hamsters (MacEwen et al. 1981). Animals were exposed for 6 hours/day, 5 days/week, for 1 year, followed by a variable observation period (12-38 months). Significant increases over controls were reported for lung adenomas in mice at the highest dose; nasal cavity adenoma and adenocarcinoma in rats; and nasal cavity polyps in hamsters. No significant increases in tumor induction were noted at the lower doses, nor were treatment-related neoplasms reported in dogs (the observation period for dogs was considered inadequate for development of neoplasms in dogs).

Occupational exposure to hydrazine has been reported to produce systemic problems to include lung and liver damage, conjunctivitis, tremors, lethargy, long-term neurobehavioral impairment, and ultimately death (HSDB 2005).

7.10.2.3 Dermal

Hydrazine is corrosive to skin, producing caustic-like, severe, penetrating burns. It will also dissolve hair. Hydrazine exposure is also suspected in a human case of epithelioid sarcoma in an individual occupationally exposed to hydrazine fuel. Hydrazine exposure has been shown to produce dermatitis and skin sensitization (HSDB 2005).

A dermal LD_{50} is reported to be 91 mg/kg in rabbits, and 190 mg/kg in guinea pigs (HSDB 2005).

7.10.2.4 Ocular

Exposure to the eyes can produce temporary blindness. Liquid splashes to the eyes can produce corneal injuries and burns (HSDB 2005).

7.10.2.5 Developmental and Reproductive

Groups of rats exposed orally during gestation to 8 mg hydrazine hydrochloride/kg body weight resulted in maternal body weight loss and mortality, along with fetal toxicity that included reduced fetal weight and viability. Although some fetuses were pale and edematous, no major congenital malformations occurred (ACGIH 2001).

A developmental toxicity study carried out in rats receiving oral doses of 0, 2.5, 5, or 10 mg hydrazine/kg from days 6-15 of gestation resulted in both maternal and fetal toxicity at the 5 and 10 mg/kg dose rates, with 2.5 mg/kg being an apparent NOEL. Developmental delays, but no terata, were seen in the fetuses (ACGIH 2001).

Eggs of the South African clawed toad (*Xenopus laevis*) in the cleavage state were exposed to hydrazine until hatching. Survival and development into normal larvae occurred at exposures below 10 mg/L. At 10 mg/L, 35% of the embryos were malformed at hatching; the effect was dose-related. Additional studies revealed that teratogenic effects appeared until neurulation. When Xenopus larvae were exposed to 1.0 mg hydrazine/L water for 120 hours, all died 24-48 hours after exposure. No significant effects on survival and development were observed after exposure to 0.1 mg/L, the next lowest concentration tested (HSDB 2005).

7.10.2.6 Neurotoxicity

Residual neurobehavioral impairment in a water quality technician was believed to have resulted from repeated exposure to hydrazine used to treat water over a period of 7 years. Memory and concentration problems became acute, and he was unable to work or remember material that he had read. Neuropsychological testing revealed deficits in specific task performance, memory, concentration, learning, judgment, and abstraction and mood problems. A computed tomographic exam showed no evidence of brain injury. The individual's condition improved gradually over the period of 4 years, but was never completely resolved (HSDB 2005).

An increase in the level of γ-aminobutyric acid (GABA) was observed in the whole brain of rats after administration of hydrazine via either intravenous, intraperitoneal, or subcutaneous routes. Changes in the concentration of this amino acid are believed caused by inhibition of pyridoxal phosphate-requiring γ-aminobutyrate transferase and glutamate decarboxylase (WHO 1987).

7.10.2.7 Genotoxicity

Mutagenicity of hydrazine has been demonstrated in both *in vitro* and *in vivo* assays, tested as hydrazine sulfate, hydrazine hydrate, or hydrazine hydrochloride. Reverse mutations were induced in the Ames assay using *Salmonella typhimurium* (Kimball 1977; Anderson and Styles 1978; McMahon et al. 1979; Tosk et al. 1979; Parodi et al. 1981; Rogan et al. 1982) and in tryptophan auxotrophs of *E. coli* (McMahon et al. 1979; von Wright and Tikkanen 1980), and in host-mediated assay with mice given a single dose of hydrazine sulfate by gavage (Simmon et al. 1979; IRIS 2009).

7.10.2.8 Carcinogenicity

Hydrazine is categorized as a probable human carcinogen (Group 2B), based upon inadequate evidence in humans, but sufficient evidence in experimental animal (HSDB 2005).

0.001% hydrazine in drinking water was administered to 50 Swiss mice/sex for their lifetimes. Lung adenomas and adenocarcinomas were induced in 24/50 of the males and 27/50 females (48-54%) (IRIS 2009; Toth 1972).

7.10.2.9 Ecotoxicology

7.10.2.9.1 Fate and Transport

Because of its miscibility with water and low predicted log K_{OC}, hydrazine is expected to be easily transported in the environment. Evaporation from wet surfaces is not expected, but is possible from dry surfaces. Hydrazine has a pKa of 7.96, indicating presence of the protonated form is likely, which will also inhibit evaporation (HSDB 2005).

If released to the atmosphere, hydrazine is expected to exist solely as a vapor. Atmospheric degradation by photochemically-induced hydroxyl radicals is expected, with a half-life estimated at 6 hours (HSDB 2005).

Because of a low K_{OW} value, the potential for bioconcentration of hydrazine appears low. Hydrazine can participate in cation-exchange reactions (HSDB 2005).

7.10.2.9.2 Ecotoxicity

Hydrazine poses a particular risk to aquatic organisms and terrestrial organisms that consume hydrazine-contaminated water. A fairly large amount of ecotoxicity information exists for hydrazine. EC_{50} values reported for green algae range from 0.5 µg/L to an upper value of about 37 µg/L depending upon species and exposure time (ECOTOX 2009).

The 48-hour EC_{50} in green algae (*Selenastrum capricornutum*) was 0.02 µL/L (0.02 µg/L). The 48-hour LC_{50} for *Daphnia pulex* is 0.19 mg/L.

The lowest 96-hour LC_{50} reported for finfish (Bluegill, *Lepomis macroshirus*) 1.08 mg/L in a static system. A 96-hour continuous flow exposure of bluegills resulted in a no-lethal-effects concentration of 0.43 mg/L (HSDB 2005).

A 96-hour LC_{50} reported for aquatic sowbugs (*Asellus sp.*) is 1.3 mg/L (HSDB 2005). Laboratory exposures of fathead minnows (*Pimephales promales*) have resulted in LC_{50} values from 8.98 mg/L for an 18-hour exposure, to a minimum of 2.25 mg/L for a 4-day exposure (Velte 1984; Brooke 1987). LC_{50} values for other higher finfish range from 0.28 mg/L for 2-day exposures of Bluegills to 1.0 mg/L for 4-day exposure of channel catfish (*Ictalurus punctatus*) and 1.17 mg/L for 1-day exposures of zebrafish (*Danio rerio*) to 3.40 mg/L for 4-day exposures of threespine sticklebacks (*Gasterosteus aculeatus*) (Brooke 1987; Harrah 1978; Hunt et al. 1981).

Toxicities of hydrazine and phenylhydrazine to embryos and larvae of zebrafish were studied under standardized conditions. Exposure to the chemical started at the blastula stage and the effect on hatching and survival were monitored for 15 days. The results showed that toxicities of phenylhydrazine to both embryos and larvae were more than for hydrazine. The LOEL for hatching with hydrazine was 0.049 mg/L, and the LOEL for survival of larvae exposed to hydrazine was 0.00035 mg/L. The NOAEL for hatching in embryos exposed to hydrazine was 0.0245 mg/L and the NOAEL for survival of larvae exposed to hydrazine was 0.00175 mg/L (HSDB 2005).

Minimum LC_{50}s for amphibians (salamanders and African clawed toads) are about 2120 µg/L for a 4-day exposure in salamanders (Slonim 1986) and 10-25 mg/L in the African clawed toad (*Xenopus laevis*) (Greenhouse 1976).

Hydrazine at levels between 50-1000 ppm in soil have been found to induce chromosome breakage in broadbean plants (*Vicia faba*) after only 2 days of exposure (Gupta and Grover 1970). Sixteen-day-old seedlings of cotton (*Gossypium hirsutum*) in a hydroponic culture were exposed to hydrazine in growth medium for 9 days at concentrations between 0 and 1000 mg/L and a temperature of 22-29ºC. Plants died within 48 hours of exposure to 300 mg/L and within 30 hours at the higher concentrations. Injury was first noted as foliar dehydration, without chlorosis or necrosis, after 9 days of exposure to 50 mg/L or within 24 hours of exposure to 300 mg/L or more (WHO 1987).

7.10.2.9.3 Degradation/Treatment

Hydrazine appears to degrade more rapidly in soil than in water, with oxidation and biodegradation as the main removal processes. In water, the half-life for hydrazine degradation is predicted to be 8.3 days. Vapor phase hydrazine will react with both photochemically-produced hydroxyl radicals and ozone. The half-life for reaction with hydroxyl radicals is predicted to be about 6 hours, while the half-life for degradation by ozone in the natural troposphere about 2 hours (HSDB 2005).

8 Discussion

8.1 Compound Summaries

8.1.1 Hydroxlyammonium nitrate [HAN]

Precise values for acute toxicity are not available, but HAN should be treated as a toxic substance, although it does not appear to be carcinogenic. Precautions must be taken in occupational health environments to prevent inhalation, dermal and ocular exposure. There is information from animals that HA, and by extrapolation HAN, may have developmental or reproductive impacts potentially leading to malformations, but not death.

A similar lack of precision is found for ecotoxicity information. The matter is somewhat complicated by the fact that HA/HAN can exist in various chemical forms, depending upon the pH and ionic environment.

8.1.2 Hydroxyethylhydrazine nitrate [HEHN]

The acute oral toxicity of HEHN compares favorably with that of hydrazine (367 mg/kg vs. 60 mg/kg in rats). Inhalation toxicity is also moderate. Ecotoxicity also appears to be relatively low, although ground water transport is highly likely. Occupational health hazard is moderate, except for the likelihood that HEHN will be a developmental or reproductive toxicant.

8.1.3 Ammonium nitrate [AN]

Assessing the impact of ammonium requires determining the impact of three separate components—the nitrate anion, change in pH from dissociation of the ammonium cation, and decomposition of the ammonium ion to release ammonia. Ammonium nitrate is relatively non-toxic as long as significant quantities are not involved. Because of its ionic nature, ammonium nitrate is readily transported in the environment, but is rapidly taken up by plants since both of the ions represent essential nutrients for plants. Over time, there is a potential for acidification of water by the ammonium cation.

8.1.4 1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]

AMTN is predicted to demonstrate low toxicity via oral, inhalation, and dermal routes of exposure. It is a possible ocular irritant, but this is a prediction at moderate confidence. AMTN is not predicted to be mutagenic, and although the carcinogenicity prediction from TOPKAT is indeterminate, a negative result in the Ames test indicates carcinogenicity is unlikely.

8.1.5 Carbohydrazide [CBZ]

CBZ is a moderately toxic solid with high aqueous solubility, but negligible vapor pressure. Inhalation toxicity is low, but the compound is an ocular irritant and dermal irritant and sensitizer. CBZ is expected to be positive in the Ames mutagenicity assay.

CBZ will have an environmental persistence of days to weeks, and is not readily biodegradable. Toxicity toward aquatic organisms is low.

8.1.6 2,2'-Bipyridyl [BP]

2,2'-Bipyridyl is acutely toxic via oral ingestion, and is predicted to be a developmental or reproductive toxicant. Inhalation toxicity is low. BP is mutagenic in the Ames test, but is not predicted to be carcinogenic. Occupational hazards are moderate to skin and eyes.

Environmental hazards are moderate to low, with toxicity toward benchmark species low, but some hazard of groundwater transport and relatively high environmental persistence.

8.1.7 1-Hydroxyethan-1,2,4-triazolium nitrate [HEATN]

HEATN is predicted to demonstrate low toxicity via oral, inhalation, and dermal routes of exposure, but is predicted to be a possible severe ocular irritant. HEATN is not predicted to be a developmental or reproductive toxicant (moderate confidence) or mutagenic. Carcinogenicity

modeling is indeterminate for HEATN, but a negative result in the Ames test (mutagenicity) indicates carcinogenicity is unlikely.

HEATN is predicted to be very water soluble and will likely not bind to soil. It is expected to be highly mobile in groundwater and will likely pose a hazard to surface and drinking water. Bioconcentration of HEATN in aquatic species is not anticipated, nor is aquatic toxicity. HEATN is predicted to biodegrade in the environment with a half-life of days to weeks.

8.1.8 Hydrazine

Hydrazine is extremely toxic to humans by all routes of exposure, and is a probable human carcinogen. In an occupational environment, complete physical protection, to include self-contained breathing apparatus, is required.

Ecotoxicity is also very high for hydrazine, although degradation in the environment appears to be relatively rapid. Release to the air, water, or soil should be proscribed.

8.2 Regulations and Standards

8.2.1 Hydroxlyammonium nitrate [HAN]

HAN is listed in Right-to-Know legislation in Pennsylvania and New Jersey (Sigma-Aldrich 2014).

8.2.2 Hydroxyethylhydrazine nitrate [HEHN]

No regulations or standards pertaining to HEHN were found.

8.2.3 Ammonium nitrate [AN]

AN is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200) and is listed as an oxidizing solid (category 3) and causes serious eye damage/eye irritation (category 2). AN is active on the Toxic Substances Control Act (TSCA) inventory notification list, as well as inventory lists in Canada, Europe, Phillippines, Japan, Australia, China, and Korea.

Releases of greater than 1% AN are reportable under Superfund Amendments and Reauthorization Act Title III Section 313 (SARA 313) Emergency Planning and Community Right-to-know Act (EPCRA).

AN is listed under the Right-to-Know regulations of Massachusetts, New Jersey, Pennsylvania, Illinois, and Rhode Island.

Releases greater than 5000 lbs (with > 0.2% combustible substances), thefts greater than 400 lbs (with > 0.2% combustible substances), or thefts greater than 2000 lbs (solid, nitrogen >=23%) are reportable under the U.S. Department of Homeland Security Chemical Facility Anti-Terrorism Standard (ThermoFisher 2019).

8.2.4 1-Methyl-4-amino-1,2,4-triazolium nitrate [AMTN]

No regulations or standards pertaining to AMTN were found.

8.2.5 Carbohydrazide [CBZ]

Carbonohydrazide is listed under the Right-to-Know regulations of Pennsylvania and New Jersey (Sigma-Aldrich 2020).

8.2.6 2,2'-Bipyridyl [BP]

BP is listed as a Community Right-to-Know compound in New Jersey and Pennsylvania (Sigma-Aldrich 2015).

8.2.7 1-Hydroxyethan-1,2,4-tirazolium nitrate [HEATN]

No regulations or standards pertaining to HEATN were found.

8.2.8 Hydrazine

Hydrazine is regulated under the Clean Air Act as a Hazardous Air Pollutant (HAP). OSHA has established an 8-hour TWA limit of 1 ppm (1.3 mg/m^3), and the ACGIH has established an 8-hour TWA TLV of 0.01 ppm. The IDLH level is 50 ppm. Hydrazine is also regarded as carcinogenic (HSDB 2005).

Releases of greater than 1 lb (0.454 kg) of hydrazine are reportable under CERCLA/SARA (Comprehensive Environmental Response, Compensation and Liability Act [Superfund]/Superfund Amendments and Reauthorization Act).

8.3 Conclusions

Table 7 provides the components of 5 propellants under development as potential replacements for hydrazine.

Table 7: Formulation Components

Formulation	Components	Percent Composition*
M315E	HEHN	34
	S-HAN5**	34
	AN	5
	2,2'-Bipyridyl	1
M315F	HEHN	73
	AN	17
	2,2'-Bipyridyl	0.3
AFRL 824S	HEATN	24
	S-HAN5**	51
	AN	5
	2,2'-Bipyridyl	1
AFRL 1107P	AMTN	20
	HEHN	5
	S-HAN5**	47
Carbohydrazide	Carbohydrazide	100

* Percent compositions brought to 100% by addition of water. **Stabilized HAN containing 1 wt% 2,2'-bipyridyl and 5 wt% AN.

The eight substances used in formulating these propellants may be ranked generally in toxicity as:

1) Hydrazine
2) 2,2'-bipyridyl
3) Carbohydrazide
4) HAN
5) HEHN
6) Ammonium nitrate
7) HEATN
8) AMTN

This ranking is based strictly on data for oral toxicity or oral toxicity predictions, but inhalation toxicity is similar in most cases. Occupational health hazards are moderate except for hydrazine. Hydrazine, 2,2'-bipyridyl, and carbohydrazide are likely mutagenic in the Ames assay. Also HAN and HEHN are predicted to be developmental or reproductive toxicants.

Ecotoxicity information is generally lacking, although carbohydrazide is relatively persistent.

9 Recommendations

More in depth experimental testing is recommended for the down-selected formulations, beginning with *in vitro* testing and progressing to *in vivo* work as indicated by circumstances.

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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

<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

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