



Toxicology Report No. S.0052729.5-18, March 2022
Toxicology Directorate

Toxicology Assessment for Safer Alternatives for Readiness (SAFR) Program
Work Unit Airborne Lead Reduction (ALR) 17-02 Reduced Lead Propellant for
the 2.75" Rocket Motor, March 2018 – December 2021

Prepared By: Mark A. Williams, Ph.D., FAAAAI, Valerie H. Adams, Ph.D., DABT,
and William S. Eck, Ph.D.
Health Effects Division

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188		
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1. REPORT DATE (DD-MM-YYYY) 31-12-2021		2. REPORT TYPE Technical Report		3. DATES COVERED (From - To) Mar 2018-Dec 2021	
4. TITLE AND SUBTITLE Toxicology Assessment for Safer Alternatives for Readiness (SAFR) Program Work Unit Airborne Lead Reduction (ALR) 17-02. Reduced Lead Propellant for the 2.75" Rocket Motor			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Mark A. Williams, Ph.D., FAAAAI William S. Eck, Ph.D. Valerie H. Adams, Ph.D. D.A.B.T.			5d. PROJECT NUMBER WBS.0052729		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER ALR 17-02		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Toxicology Directorate U.S. Army Public Health Center Aberdeen Proving Ground, MD 21010			8. PERFORMING ORGANIZATION REPORT NUMBER S.0052729.5-18		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Combat Capabilities Development Command (DEVCOM) Safer Alternatives for Readiness (SAFR) Program 3071 Aberdeen Boulevard Aberdeen Proving Ground, MD 21005			10. SPONSOR/MONITOR'S ACRONYM(S) DEVCOM-SAFR		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S) ALR 17-02		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for Public Release, Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT This report updates "Toxicology Report No. S.0002754e-13, 2.75" Rocket Propellant Transition, Work Unit RM 11-06, published September 2013" and includes the revised formulation for the RPD-640 propellant wherein aluminum was removed and the ballistic modifier LC-12-15 (copper, β -resorcylate salicylate lead complexes) replaced bismuth subsalicylate. The revised report describes potential health and/or environmental hazards associated with elemental lead and copper contained within the LC-12-15 mixture and any updated toxicity information for the other constituents.					
15. SUBJECT TERMS Lead, resorcylate, LC-12-15, Rocket Propellant, ballistic modifier					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 77	19a. NAME OF RESPONSIBLE PERSON Valerie H. Adams
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (Include area code) 410-436-3980

ACKNOWLEDGEMENTS

The authors acknowledge the support and encouragement provided to this effort by Ms. Kimberly Watts, Director, U.S. Army Combat Capabilities Development Command (DEVCOM), Safer Alternatives for Readiness (SAFR) Program, and Dr. John La Scala of the Environmental Quality Technology (EQT) Program, Pollution Prevention Technology Team (P2TT). The authors thank Dr. Glenn Leach for his scientific review and Ms. Desiree Harris for technical review.

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TOXICOLOGY REPORT NO. S.0052729.5-18
TOXICOLOGY ASSESSMENT FOR SAFR PROGRAM WORK UNIT ALR 17-02:
REDUCED LEAD PROPELLANTS FOR GREEN 2.75" ROCKET MOTOR
MARCH 2018 – DECEMBER 2021

1. SUMMARY

1.1 Overview

Research, development, testing, training, and use of substances potentially less hazardous to human health and the environment are vital to U.S. Army readiness. Safeguarding the health of Soldiers, Civilians, and the environment requires an assessment of alternatives before they are fielded. Continuous assessments initiated early in Research, Development, Testing, and Evaluation (RDT&E) processes can save significant time and effort during RDT&E, and over the life cycle of the items developed. Residues of pyrotechnics, propellants, explosives, and incendiaries that cost the U.S. Army billions of dollars and were part of mission essential activities have been found in soil, air, surface, and groundwater samples, creating environmental problems and interfering with training activities.

1.2 Purpose

This report updates Toxicology Report No. S.0002754e-13, 2.75" Rocket Propellant Transition, Work Unit RM 11-06, published September 2013 and includes the revised formulation for the RPD-640 propellant wherein aluminum was removed and the ballistic modifier LC-12-15 (copper, β -resorcylate salicylate lead complexes) replaced bismuth subsalicylate. The revised report describes potential health and/or environmental hazards associated with elemental lead and copper contained within the LC-12-15 mixture and any updated toxicity information for the other constituents.

1.3 Conclusions

Toxicological and physical-chemical properties were obtained and reviewed for the individual chemicals used in this formulation to assess potential concerns relating to environmental quality or human health from exposure to the formulation. Some data gaps were noted that should be addressed as development continues. The presence of lead, a known toxic metal, in LC-12-15 is of special concern. However, it is listed as a minor constituent of the formulation and the quantity of use will determine the degree of hazard.

1.4 Recommendations

Given the available data, the modified formulation exhibits moderate potential of adversely affecting human health and the environment. Toxicity data gaps exist for di-n-propyl adipate (DNPA) and 2-nitrodiphenyl amine (2-NDPA). Both DNPA and 2-NDPA are minor constituents and are anticipated to combust during use of the system. The resorcylate/salicylate constituents are also expected to combust during use of the system. The lead and copper elements will not

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combust and exhaust plumes should be analyzed for lead and copper and Soldier exposure to these plumes should be addressed. Based on the toxicology review, Environment, Safety, and Occupational Health (ESOH) hazards do not restrict the continued development of the system; however, continued review for potential lead and copper exposure and environmental contamination is recommended.

2. REFERENCES AND GLOSSARY

See Appendix A for a comprehensive list of references. See the glossary for commonly used terms and acronyms.

3. AUTHORITY

Funding for this work was provided under Military Interdepartmental Purchase Request No. #11057946. This Toxicology Assessment addresses, in part, the ESOH requirements outlined in Army Regulation (AR) 200-1, AR 40-5, and AR 70-1, Department of Defense Instruction (DoDI) 4715.4, and Army Environmental Requirement and Technology Assessment (AERTA) PP-3-02-07, Compliant Munitions Lifecycle for Warfighter Readiness (DA 2007, 2017, 2020; DOD 1998; AERTA 2018). The Sponsor is the Combat Capabilities Development Command (DEVCOM) Safer Alternatives for Readiness (SAFR) Program. The Principle Investigator is Dr. Gregory Drake, U.S. Army DEVCOM Aviation and Missile Center (AvMC), Huntsville, Alabama.

4. BACKGROUND

Current regulations require assessment of human health and environmental effects on exposure to substances in the soil and surface or groundwater. Assessments conducted after an item is fielded have identified adverse environmental and human health effects that must be addressed, often at substantial cost. It is more efficient to conduct ESOH assessments early in the RDT&E process in order to avoid unnecessary costs, conserve physical resources, and sustain the health of Soldiers, Department of the Army (DA) Civilians, and others. In an effort to support this preventive approach, the U.S. Army Public Health Center (APHC) has been tasked with creating a phased process to identify ESOH effects that can impact 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

Lead is used as a ballistic-modifier compound in rocket and missile propellant formulations. Lead is an environmentally persistent toxic metal, absorbed via ingestion and inhalation, and the modes and mechanisms of toxicity are known. Lead exposure can damage the circulatory, alimentary, reproductive, and nervous systems, and is a confirmed teratogen and developmental toxicant. Exposure to lead used in the propellant formulations of projectiles and rockets of all sizes has the potential to affect the health of Soldiers and DA Civilians. Similarly, rocket/missile propellant formulations contain copper as a ballistic modifier. Like lead, copper-containing compounds have the potential for toxicity, particularly in the context of gastrointestinal toxicology in exposed individuals.

In this updated report, the potential for adverse health effects and environmental impacts from exposure to the modified RPD-640 formulation, which includes the copper and lead containing LC-12-15, are summarized. The objective of this work unit is to comparatively demonstrate the performance of a reduced-lead propellant with that of the current lead-based propellant.

6. METHODS

To determine the human health and environmental impact of compounds employed in novel formulations, each compound needs correct identification and its physical, chemical, and toxicological properties assessed. Table 1 provides the compound names, percent formulation, and CASRN for the formulation. While not all compounds possess a CASRN, it can be used as a keyword to interrogate online databases that are often cross-referenced with systematic and trivial (i.e., “common” or non-systematic) chemical substance names. In some cases, synonyms and trade names are used to identify structures. For compounds that do not have a CASRN, the simplified molecular-input line-entry system (SMILES) is generated with EPISuites (Estimation Programs Interface (EPI) Suite™) (U.S. Environmental Protection Agency (EPA) 2013) and searched in PubChem (Kim et al. 2019; National Center for Biotechnology Information (NCBI) 2020) to identify compounds that may have been submitted (e.g., for patent purposes) but were not in commerce. For each compound, SMILES is used to generate the physico-chemical properties.

Table 1. Target Formulation Components (% Formulation is Proprietary)

Chemical Substance	CASRN	Function
Nitrocellulose (12.2% nitrogen)	9004-70-0	Binder/fuel/oxidizer
Nitroglycerin	55-63-0	Oxidizer/plasticizer
Triacetin	102-76-1	Fuel/plasticizer
Di-n-propyl adipate (DNPA)	106-19-4	Fuel/plasticizer
2-Nitrodiphenyl amine (2-NDPA)	119-75-5	Stabilizer
Candelilla wax	8006-44-8	Fuel/processing aid
Carbon black	7440-44-0	Ballistic modifier
<u>LC-12-15</u> Lead, Copper, beta-resorcylate salicylate complexes	68411-07-4	Ballistic modifier

The properties necessary to assess environmental fate and transport include:

- Molecular weight (MW) (in grams (g) per mol; g/mol)
- Boiling point (bp) in degrees Celsius (°C)

- Octanol-water partition coefficient ($\log K_{OW}$)
- Organic carbon partition coefficient ($\log K_{OC}$)
- Water solubility (milligrams (mg) or milliliters (mL) per liter (L) e.g., mg/L or mL/L)
- Henry's Law constant (K_H)
- Vapor pressure (vp) in millimeters (mm) of mercury (Hg) – mmHg

Basic physical and chemical properties are usually determined by consulting tertiary sources when such information is available. Where these data were unavailable, predictions from EPI Suites were used.

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, carcinogenicity; and mode(s) and mechanisms of toxicity. Values reported herein include lethal dose 50% (LD_{50}) (reported in milligrams per kilogram (mg/kg)), no observed adverse effect level (or concentration) (NOAEL/C), lowest observed adverse effect level (or concentration) (LOAEL/C) reported in mg/kg or mg/liter (mg/L), 50% effect concentration (EC_{50}), 50% inhibitory concentration (IC_{50}), lethal concentration 50% (LC_{50}) typically reported as mass (g or mg) per cubic meter (m^3) or mg/L, clinical chemistry values may be reported in deciliters (dL) and some water quality values may be reported in micrograms/liter ($\mu g/L$) or parts per million (ppm). Toxicological information was derived directly from primary sources whenever possible. Where data gaps exist, *in silico* toxicity estimates were made using two quantitative structure activity relationship (QSAR) programs: TOPKAT[®] (Toxicity Prediction Komputer Assisted Technology) (BIOVIA 2015) and ECOSAR[™] (ECOLOGICAL Structure Activity Relationship) (EPA 2012). Data acquired from the TOPKAT model provides confidence intervals and goodness-of-fit information for each endpoint so that qualitative estimates and comparisons between chemicals can be given. The ECOSAR program provides point estimates for aquatic endpoints (green algae, Daphnia, and fathead minnow acute toxicity and chronic values).

Sources used in this search included The Merck Index (O'Neil 2006); the National Institutes of Health (NIH), the EPA, the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR), the EPA ECOTOXicology Database System (ECOTOX), and the Defense Technical Information Center (DTIC[®]). Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health Organization (WHO), and the International Agency for Research on Cancer (IARC). Primary references are identified and retrieved by PubMed[®] and the EBSCOhost[®] Research Databases.

In December 2019, the National Library of Medicine (NLM) was reorganized and most of the toxicology information services available through TOXNET were integrated into other NLM products and services. Prior to December 2019, TOXNET provided links to a suite of individual databases including ChemIDplus[®] (chemical structures, registration numbers, and links to other sites providing physical chemical properties of the compound), the Hazardous Substances Data Bank (HSDB[®]), TOXLINE (references to literature on biochemical, pharmacological, physiological and toxicological effects of drugs and other chemicals), the Developmental and Reproductive Toxicology (DART) database, the Comparative Toxicogenomics Database (CTD),

the Integrated Risk Information System (IRIS), and the Animal Testing Alternatives (ALTBIB) database, as well as several others, including the archived databases for the Chemical Carcinogenesis Research Information System (CCRIS), the Carcinogenic Potency Database (CPDB), and GENE-TOX genetic toxicity database. In some instances, commercial suppliers may provide results of in-house research that does not appear in the open literature and are protected by confidentiality rules; these data are not reported in the toxicity assessment (TA) but are retained by APHC.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general risk categories (low, moderate, or high) using defined criteria modified from the previously published work of Howe et al. (Howe et al. 2007). Appendix B, Table B-1 describes the criteria used in the categorical definitions of risk. Where applicable, the global harmonized system (GHS) is also used to categorize risk; additional information is found in Appendix B, Section B-2. For the final assessment, the percent formulation for each substance was also considered. If no experimental data were identified from the literature, then the QSAR estimates were used.

7. RESULTS

7.1 Physical and Chemical Properties

Physical and chemical properties of the formulation are summarized in Appendix C, Table C-1. When data were not found, the acronym "nd" (no data) is used. In some cases, the property name is not applicable ("n/a") to the described substance. For example, if a particular compound is a non-volatile 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 Appendix C, Table C-2. Assessments of human health and environmental toxicity for each of the formula components are presented in Section 8. Each characterization is generally based on the criteria set forth in Appendix B, Table B-1. Where applicable, the GHS categories are included in the assessment (see Appendix B, Section B-2 for details). 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.

7.3 Nitrocellulose [NC]

7.3.1 General Information

Military-grade nitrocellulose (NC) contains more than 11.6% nitrogen by mass, and approaches the trinitrated form of the glucose monomer. The NC used in this formulation contains 12.2% nitrogen. NC does not appear to be absorbed into the body by any route (Hartley et al. 1992). In addition to its explosives/propellant applications, less-nitrated NC is used in solutions of ethyl alcohol and/or diethyl ether as a topical adhesive and protectant for cuts and small burns (O'Neil 2006). The U.S. Food and Drug Administration (FDA) recognize collodion (a formulation containing NC) as an indirect food additive to be used only as a component of packaging

adhesives. When burned as a propellant component, NC can potentially form toxic oxides of carbon, nitrogen, and hydrogen cyanide (Kim et al. 2019; NCBI 2020). NC is resistant to biological degradation and is persistent in the environment. Alkaline hydrolysis of NC appears to yield products that can be decomposed by microbial activity (U.S. Army Corp Engineers 1998). Data gaps for NC cannot be modeled by current QSAR techniques due to the polymeric nature of the molecule.

7.3.2 Toxicology Data

7.3.2.1 Oral

The acute oral LD₅₀ in rats is reported to be >5,000 mg/kg, suggesting low toxicity associated with oral exposures of NC (Imperial Chemical Industries Inc. (ICI) 2002). The LD₅₀ for mice also exceeds 5,000 mg/kg (Kim et al. 2019; NCBI 2020).

No adverse effects that could be related to nitrocellulose were identified in 13-week studies of dogs, rats, and mice (Ellis et al. 1976).

Long-term (2-year) studies (Ellis et al. 1980) conducted in dogs, rats, and mice have indicated a dose-dependent increase in total feed consumption, and decreased weight gain in animals that received 10% nitrocellulose in the feed. At 10% content by weight, the effect of bulk fiber mass becomes more important than the chemical nature of the compound. Necropsy of animals being fed at this level often revealed the presence of cotton fiber masses that block the digestive tract, which interfered with normal digestion that resulted in malnutrition and increased feeding to overcome hunger. Rats receiving cotton fiber at this level (10%) will fill their enclosures with fiber taken from the food ration, making it impossible to compute dose rates.

7.3.2.2 Inhalation

NC might be a mucous membrane and upper respiratory tract irritant (NCBI 2020).

7.3.2.3 Dermal

NC is a dermal irritant (NCBI 2020). NC, when in close contact with skin, may enhance dermal penetration of co-occurring chemicals (Kim et al. 2019; NCBI 2020).

7.3.2.4 Ocular

NC causes eye irritation (NCBI 2020).

7.3.2.5 Development and Reproduction

Three-generation studies in rats indicated that NC administered alone in the diet did not adversely affect reproduction. However, the increased inert bulk of 10% fibers (NC or cotton linters) may reduce the lactation index and pup weight (Hartley et al. 1992).

7.3.2.6 Genotoxicity

Salmonella typhimurium test strains TA1535, TA1537, TA1538, TA98, and TA100 were exposed to nitrocellulose at levels of 100, 1,000, and 5,000 µg/plate for 48 hours. In this assay, all results were negative, either with or without S9 microsomal activation (Ellis et al. 1976; Hartley et al. 1992). Cytogenetic effects were studied in rats that were fed nitrocellulose at 10% of the feed mass. No changes in chromosomal frequency distribution, tetraploidy, frequency of chromosome breaks, gaps, or translocations in either blood lymphocytes or kidney cells were seen (Ellis et al. 1976).

7.3.2.7 Carcinogenicity

Long term (2-year) studies in dogs, rats, and mice failed to find an increased incidence of tumors as compared to control animals (Ellis et al. 1980).

7.3.2.8 Neurotoxicity

Formulations of NC may have a central nervous system (CNS) depressant effect but this is likely due to the ethyl ether and/or ethanol components that comprise the common NC solution known as collodion (e.g., CNS solvent syndrome) (NCBI 2020). Prolonged exposure can result in nausea, headache, and vomiting.

7.3.3 Ecological Data

7.3.3.1 Fate and Transport

Due to its insolubility, NC is immobile in groundwater. Partition to the atmosphere is impossible due to the high-molecular-weight-polymer nature of this material; presence in the atmosphere would be in the form of particulates. NC will not bioaccumulate.

7.3.3.2 Ecotoxicity

A 96-hour toxicity bioassay using fathead minnow gave an $LC_{50} > 10,000$ mg/L (ICI 2002). No acutely toxic effects of nitrocellulose were observed among fish, invertebrates, or algal species with the exception of the green algae *Selenastrum capricornutum*. Sediments that contained nitrocellulose indicated no adverse effects among Chironomid populations that were exposed to 540 mg/kg of sediment over two generations (U.S. Army Medical Research and Development Command (USAMRDC) 1976).

Four species of invertebrates and four species of fish were unaffected by nitrocellulose concentrations as high as 1,000 mg/L. Four species of algae were exposed to concentrations up to 1,000 mg/L. Three were unaffected, but *S. capricornutum* showed a 96-hour EC_{50} of 731 mg/L (Sullivan et al. 1978).

7.3.3.3 Degradation and Treatment

NC is subject to degradation by alkali treatment. Storage of dry NC results in decomposition

over time (Kim et al. 2019; NCBI 2020). In addition, NC degradation involves a complex chemical dissociation into a wide variety of products. Extremely high concentrations of nitrate and nitrite ions are present in leachates from NC landfills. Low permeability of landfill sludge and especially mixtures of soil/sludge will attenuate the effect over a long period of time (Kim et al. 2019; NCBI 2020).

7.4 Nitroglycerin [NG]

7.4.1 General Information

Also known as glyceryl trinitrate (GTN), trinitroglycerin, trinitroglycerine, 1,2,3- trinitroxypropane, and 1,2,3-propanetriol trinitrate, nitroglycerin (NG) is a colorless, oily, explosive liquid obtained by nitrating glycerol (Figure 1). Since the 1860s, it has been used as an active ingredient in explosives, specifically dynamite. It is also used in some solid propellants, such as cordite and ballistite. In its pure form, it is a primary contact explosive (physical shock can cause it to explode) and degrades over time to even more unstable forms. This makes NG highly dangerous to transport or use. In this undiluted form, it is one of the most powerful explosives.

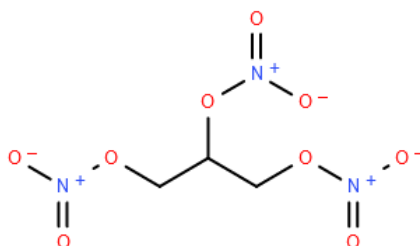


Figure 1. Nitroglycerin

NG is also used medically as a vasodilator to treat heart disease such as angina and chronic heart failure, where it mediates the release of nitric oxide. NG has profound effects on systemic and cardiac microcirculation. Its actions are signaled via soluble guanylate cyclase activation in vascular smooth muscle cells. Long-term industrial NG exposure has been associated with withdrawal symptoms and sudden death from cardiovascular events (Klaassen 1996). The main adverse effects of NG are those shared by all nitrate esters including hypotension, reflex tachycardia, and palpitations. Postural hypotension and syncope (fainting) are also seen, especially in the elderly. Rarely, severe bradycardia is seen and throbbing headache is common. In addition, methemoglobinemia is possible and tolerance might likely develop over time (NCBI 2021b).

7.4.2 Toxicology Data

7.4.2.1 Oral

In the CompTox database, the oral LD₅₀ was reported to be approximately 510–822 mg/kg in rats and 895–1188 mg/kg in mice (Williams et al. 2017). The rat 822 mg/kg and mouse 1,188 mg/kg NG are reported in the HSDB entry (NCBI 2021b).

A series of subacute and chronic toxicity tests in several species were reported by Ellis, et al. (Ellis et al. 1984). Dogs given up to 200 mg/kg-day for 5 days had transient and dose-related severe methemoglobinemia; behavioral depression was observed in the 200 mg/kg-day dose group. No adverse effects were seen in dogs given up to 1 mg/kg-day of NG for 4 weeks. In these animals, no adverse effects were observed when the dose was increased to 5 mg/kg-day for 9 more weeks. When the exposure was extended to 12 months, dogs given 1, 5, or 25 mg/kg-d had transient and dose-related mild methemoglobinemia (Ellis et al. 1984).

Rats fed 0.1% NG for 5 weeks did not have adverse effects; however, when the dose was increased to 0.5% (230–234 mg/kg-day) for 8 more weeks, decreased feed consumption and decreased weight gain were observed. Rats fed 2.5% NG for 13 weeks (1,406 or 1,416 mg/kg-day for males and females, respectively) had transient weight loss, compensated anemia, and testicular degeneration (Ellis et al. 1984). No adverse effects were seen in a similar split dose study with mice fed 0.1% NG for 3 weeks then 0.5% NG for 10 additional weeks (Ellis et al. 1984).

Rats fed 1% NG for 2 years (363 or 434 mg/kg-day for males and females, respectively) exhibited decreased weight gain, decreased grooming, methemoglobinemia (and sequelae), cholangiofibrosis, hepatocellular carcinoma, and interstitial testicular cell tumors (Ellis et al. 1984). NG treated females had decreases in the incidence of naturally occurring pituitary chromophobe adenomas and mammary tumors that resulted in increased the life span in these animals.

In a 2-year feeding study, mice fed 1% NG (1,022 or 1,058 mg/kg-day for males and females, respectively) had weight loss, decreased grooming, and methemoglobinemia with associated sequelae (Ellis et al. 1984).

7.4.2.2 Inhalation

Inhalation of dust may cause toxic effects similar to ingested effects (Kim et al. 2019; NCBI 2021b).

7.4.2.3 Dermal

Nitroglycerin is absorbed through intact skin at levels sufficient to cause vasodilatation and toxicity. In humans, the most prominent manifestations of NG toxicity are severe headache and adverse cardiovascular events, which include organic nitrate dependence in the case of chronic exposure (Gilman et al. 1990). NG was reported to be a moderate sensitizer in guinea pigs (Lee et al. 1977).

7.4.2.4 Ocular

Ocular toxicity of three NG containing ointments were evaluated in rabbits (Zalta et al. 1985). Rabbits received ointment twice a day for 21 days. Mild conjunctival chemosis (swelling) was observed for all three NG ointments during treatment that was resolved by day 22. NIOSH recommends wearing eyewear that is appropriate to preventing eye contact with NG (NCBI 2021b).

7.4.2.5 Development and Reproduction

Developmental and reproductive studies in animals have failed to demonstrate that NG is a teratogen. However, exposure to high NG concentrations might result in testicular lesions, male infertility, and delayed development of offspring (National Technical Information Service 1986).

A three-generation reproductive toxicity study in rats showed no effect on fertility or viability, growth, and development of offspring at doses up to 38 mg/kg-day (NCBI 2021b). Adverse fertility effects were seen at doses above 363 mg/kg-day that were secondary to malnutrition and testicular tumors.

Developmental studies were conducted in rats and rabbits that were given intravenous doses of up to 20 and 4 mg/kg-day, respectively, during typical gestation administration periods (NCBI 2021b). No teratogenic, embryotoxic, or fetotoxic effects were observed.

Using a quail egg test system, NG was found to induce malformed viable embryos (Bardai et al. 2011). Dose dependent increases in microphthalmia, craniofacial, heart and neural tube defects were observed in eggs injected with 0.88–440 micromolar (μM) NG. In follow-on experiments, the presence of nitrated proteins suggested that reactive nitrogen species were generated, disrupted the redox status and led to malformations in the embryos (Bardai et al. 2013).

7.4.2.6 Genotoxicity

There was no evidence of mutagenicity in an *in vivo* dominant lethal assay with male rats that were treated orally with doses of up to approximately 363 mg/kg-day, or in *ex vivo* cytogenetic tests in rat and dog tissues (Kim et al. 2019; NCBI 2021b). NG has had mixed results in the Ames assay with weak positivity in strain TA1535 in the presence of liver microsomes (NCBI 2021b; EPA 2003).

NG was non-mutagenic after exposure of Chinese hamster (K-1) cells (CHO-K1), and was negative in male and female rat chromosome aberration assays after subchronic and chronic exposure (Lee et al. 1977; EPA 2003).

7.4.2.7 Carcinogenicity

NG is not listed as a carcinogen by the IARC (IARC 2021).

7.4.2.8 Neurotoxicity

No experimental data were found. NG is not anticipated to be a neurological hazard. Headaches caused by NG are due to cerebral vasodilation (Tfelt-Hansen and Tfelt-Hansen 2009).

7.4.3 Ecological Data

7.4.3.1 Fate and Transport

NG is expected to adsorb to suspended solids and sediments if released to the water due to a log K_{OC} value of 2.25, and not pose a hazard to surface or drinking water (EPA 2013). Volatilization from surface water is not expected. With a vapor pressure of 2.0×10^{-4} mmHg at 20 °C, NG is expected to exist in both vapor and particulate phases in the atmosphere (EPA 2013). Vapor phase NG is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of 15 days.

Particulate phase NG may be removed from air by wet or dry deposition. NG weakly absorbs light at a wavelength of >290 nanometers (nm), and might be subject to direct photolysis; however, the kinetics of this process remain poorly understood (Kim et al. 2019; NCBI 2021b).

With an estimated log BCF (bioconcentration factor) of 0.60, the potential for bioconcentration in aquatic organisms is low. Hydrolysis of NG is expected to be an important environmental fate process under alkaline conditions (Kim et al. 2019; NCBI 2021b).

7.4.3.2 Ecotoxicity

In the late 1970s, the U.S. Army commissioned studies to characterize the aquatic toxicity of nitroglycerin and used these data to derive proposed water quality criteria (USAMRDC 1978). These data are also reported in the ECOTOX database (EPA 2008). The 96-hour LC_{50} was 1.90 mg/L in rainbow trout, 1.28 mg/L in bluegill, and 3.58 mg/L in the fathead minnow. In 96-hour tests using *Daphnia*, when the dosing media was renewed, the LC_{50} was 17.8 mg/L; immobilization in static conditions occurred at 50 mg/L (EPA 2008). The 96-hour EC_{50} for alga (*S. capricornutum*) was determined to be 1.15 mg/L (EPA 2008).

In quail (*Colinus virginianus*), an 8-day feeding study was conducted. The LD_{50} was >5,620 ppm-feed with an LOAEL of 5,620 ppm and an NOAEL of 3,160 ppm; internal doses of NG were not measured (Fink et al. 1980).

7.4.3.3 Degradation and Treatment

NG was completely biodegraded in 13 days using river water and river water/sediment microcosms that were obtained from a river near a munitions facility in Virginia (Kim et al. 2019; NCBI 2021b). NG may undergo photolysis in water slowly in sunlit surface water. The half-life of NG with a starting concentration of 5.8 ppm in distilled water, filtered river water, and filtered pond water that was exposed to sunlight was 116, 57, and 73 days, respectively (Kim et al. 2019; NCBI 2021b).

NG and other aliphatic nitric acid esters readily undergo aerobic biodegradation via successive removal of nitrate groups to isomeric derivatives. Results of a shake flask test that was run at 30 °C with activated sludge inoculums showed a 53.6% loss of NG in 5 days. In a continuous bench-scale activated sludge apparatus, a mean reduction of 92.2% was obtained. NG was unsuitable as a biodegradable source of carbon and nitrogen; thus, supplementation with additional carbon and nitrogen is necessary (Kim et al. 2019; NCBI 2021b). Complete mineralization of NG was achieved within 4 days using mixed cultures and an anaerobic digester using digester sludge from a municipal wastewater treatment plant amended with 2 g/L of glucose (Kim et al. 2019; NCBI 2021b).

7.5 Triacetin

7.5.1 General Information

Triacetin is the triacetate ester of glycerol and has uses as a solvent in the manufacture of celluloid photographic films, as a fixative in perfumery, and as a solvent in many types of dyeing and tanning (Figure 2). It also has clinical utility as a topical anti-fungal (O'Neil 2006).

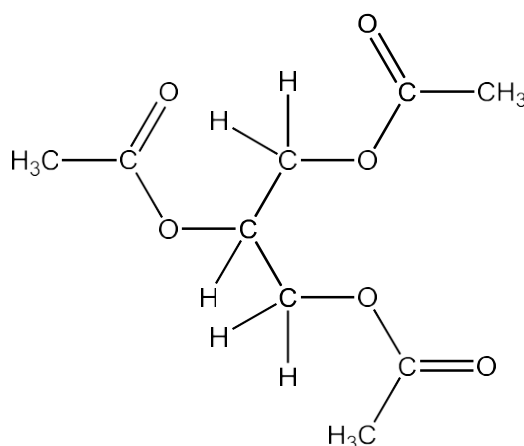


Figure 2. Triacetin

7.5.2 Toxicology Data

7.5.2.1 Oral

According to the FDA, triacetin is Generally Recognized as Safe (GRAS) as a human food ingredient. Triacetin was found to be nontoxic to animals in acute oral exposures (Fiume 2003). Triacetin was nontoxic to animals in subchronic feeding studies (Fiume 2003). The oral LD₅₀ in mice was 1,100 mg/kg and 3,000 mg/kg in rats (NCBI 2021c).

Triacetin is the triglyceride of acetate and can potentially serve as a caloric agent; thus, triacetin has been extensively studied for its role in parenteral nutrition (Bailey et al. 1991; Bleiberg et al.

1993; Karlstad et al. 1992). Infusing dogs with triacetin showed no overt toxicity but did promote significant increases in ketone body production and concentration. Similarly, rats supplied with triacetin as part of a nutritionally balanced parenteral formulation had no overt toxic effects and nitrogen balance was improved compared with control animals (Bailey et al. 1992).

7.5.2.2 Inhalation

Triacetin was not toxic to animals in acute inhalation studies (Fiume 2003). The rat 4-hour LC₅₀ is reported as >1.72 g/m³ (European Chemical Agency (ECHA) 2021g).

7.5.2.3 Dermal

Triacetin was not toxic to animals in dermal studies, except in one study where it was reported to cause erythema, slight edema, alopecia, desquamation, and some slight irritation in rabbit eyes. It was not sensitizing in guinea pigs and only slightly irritating to guinea pig skin (Fiume 2003). A (hyperbaric) Duhring chamber test was conducted on 20 healthy volunteers. Triacetin was applied at a 50% dilution for 24 hours. Only very mild skin irritation was observed. In humans, triacetin reportedly has caused ocular irritation but without evidence of injury (Fiume 2003).

7.5.2.4 Ocular

Triacetin is a slight to moderate ocular irritant (NCBI 2021c).

7.5.2.5 Development and Reproduction

Triacetin is quickly metabolized to glycerol and acetic acid, neither of which are developmental toxicants (Fiume 2003). Triacetin is predicted as negative for developmental toxicity using TOPKAT.

7.5.2.6 Genotoxicity

Triacetin is nonmutagenic, being quickly metabolized to acetic acid and glycerol. In adult *Drosophila*, a dose of 0.2–0.3 mg had a spontaneous mutation rate of approximately one per 750 chromosomes (Fiume 2003). Triacetin was negative in the four primary *Salmonella* strains in the Ames assay, with or without metabolic activation, at concentrations of up to 5,000 µg/plate (Fiume 2003).

7.5.2.7 Carcinogenicity

No experimental data were found. Triacetin is not anticipated to be a human carcinogen and it is negative by TOPKAT.

7.5.2.8 Neurotoxicity

No experimental data were found. Triacetin is not anticipated to be a neurological hazard.

7.5.3 Ecological Data

7.5.3.1 Fate and transport

Based upon a log K_{OC} of 1.52 and an aqueous solubility of 5.08×10^4 mg/L, triacetin is expected to be highly mobile in groundwater and soil (EPA 2013). Hazard to ground and surface water is mitigated by physical and biological degradation. In the atmosphere, triacetin is expected to exist only in the vapor phase, where it is subjected to hydrolysis by photochemically-produced hydroxyl radicals. Photolysis is not expected due to a lack of light absorbance below a wavelength of 290 nm. Bioaccumulation is not expected, due to a log BCF = 0 (EPA 2013).

7.5.3.2 Ecotoxicity

Triacetin displayed an oral LD_{LO} of 150 mg/kg in frogs (ChemIDplus 2009). In a gavage study, common carp (*Ciprinus carpio*) received an oral dose comparable to approximately 122–184 mg/L and survived 2.75 days (Loeb and Kelly 1963). The EC_{50} in *Daphnia magna* was 770 mg/L and the NOEC in cocepods was 468 mg/L (Williams et al. 2017).

7.5.3.3 Degradation and Treatment

Triacetin is readily biodegraded by activated sewage sludge innocula. Triacetin undergoes base-catalyzed hydrolysis via a second order mechanism in alkaline media and the half-life is 130 days at pH 7.0 and 12 days at pH 8.0 (Kim et al. 2019; NCBI 2020).

7.6 Di-n-propyl Adipate [DnPA]

7.6.1 General Information

Di-n-propyl adipate (also known as dipropyl adipate or dipropyl ester), is used in the production of cosmetics as an odorant and is used as a bitter flavor additive for baked goods and non-alcoholic beverages (The Good Scents Company 2009) (Figure 3). DnPA is considered GRAS at a maximum concentration of 500 ppm when used in food (Smith et al. 2009).

There are few toxicity data for DnPA; however, there are data available for related diester adipic acid chemicals. Where available and pertinent, toxicity data for diethyl adipate (DEA), dibutyl adipate (DBA), di-n-octyl adipate (DnOA) and bis(2-ethylhexyl) adipate (BEHA) are provided in this report.

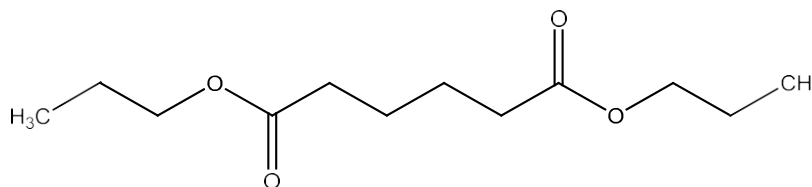


Figure 3. Di-n-propyl Adipate [DnPA]

7.6.2 Toxicology Data

7.6.2.1 Oral

In mice, preliminary studies established an acute LD₅₀ for adipic acid of 1,900 mg/kg orally, and 680 mg/kg when given intravenously. When studied in rats, the intraperitoneal (IP) LD₅₀ of adipic acid was 275 mg/kg (ECHA 2021c). This same group also fed adipic acid to rats at dietary levels of 0.1–5.0% (representing an intake of 50–2,500 mg/kg-day) for 2 years (ECHA 2021c). From this work, the only abnormality detected was reduced growth at levels of 3.0% or more of adipic acid (or 1,500 mg/kg-day).

In a related study, increased mortality, diarrhea, and reduced growth were noted in rats given a dietary level that was equivalent to 16 or 11.4 g/kg-day for 5 or 33 weeks, respectively (ECHA 2021c). These effects were seen during the first 2 weeks of exposure, after which surviving animals recovered but histological changes in the liver, kidneys, and intestine were reported. However, these effects were not evident at a dose level of 5.7 g/kg-day (ECHA 2021c).

No data were found for DnPA. The DnOA LD₅₀ values for rat and mouse were 9,110 and 15,000 mg/kg, respectively (Kim et al. 2019; NCBI 2020) and the LD₅₀ value for DEA in the rat is 1,600 mg/kg (Kim et al. 2019; NCBI 2020). The LD₅₀ for DBA is 12,900 mg/kg (rat) and 16,890 mg/kg (mouse) (NCBI 2021a). TOPKAT computational modeling analysis have provided a rat LD₅₀ of 6,600 mg/kg for DnPA. Furthermore, TOPKAT modeling predicts an LOAEL of 662.1 mg/kg-day at high confidence.

7.6.2.2 Inhalation

No data were found for DnPA. TOPKAT modeling predicts an LC₅₀ of 20 g per cubic meter (g/m³)-hour for DnPA. The rat acute 4-hour LC₅₀ for DBA is 3.2 g/m³ and the mouse 2-hour acute LC₅₀ was reported as >17 mg/m³ (NCBI 2021a).

7.6.2.3 Dermal

No data were found for DnPA. TOPKAT predicts DnPA will be neither a skin irritant nor sensitizer. The structurally related DBA is used on dogs and clothing as a repellent against chiggers and ticks (Gosselin et al. 1984). Other structurally similar molecules are used in lotions, indicating a low potential for adverse skin effects.

7.6.2.4 Ocular

Experimental data not found. TOPKAT models do not predict DnPA to be an ocular irritant.

7.6.2.5 Development and Reproduction

Adipic acid esters were shown to be teratogenic in rats by a single research group; however, these results could not be reproduced (Schardein 1993). TOPKAT modeling predicts that DnPA will not be a developmental or reproductive toxicant at high confidence. However, in a 1973 study by Singh et al., seven adipates (i.e., dimethyl, diethyl, dipropyl, diisobutyl, di-n-butyl, di-2-

ethylhexyl, and dicyclohexyl) were evaluated for their potential embryonic-fetal toxicity and teratogenic effects in rats (Singh et al. 1973). Adipate ester acute toxicity was assayed by intraperitoneal delivery of graded doses of these chemicals in rats and observing the animals for mortality over 7 days. In reproductive studies, female rats were intraperitoneally administered adipate esters at four dose levels of one-thirtieth, one-tenth, one-fifth, and one-third of their acute LD₅₀ values for each injection on the 5th, 10th and 15th days of gestation. Subsequent studies were conducted on the 20th day of gestation after euthanizing rats (Singh et al. 1973). In the Singh et al. study, fetal resorption rates of 20% were seen at one-third of the LD₅₀ dose level for dipropyl adipate. However, fetal resorption rates decreased markedly according to the diethyl adipate dose, with the lowest incidence found at a dose of one-thirtieth the LD₅₀ value (1.9%). Although fetal deaths were observed at lowered frequency and in smaller numbers than the other criteria considered, two demised fetuses (or 3.6%) were found in the group that had received one-third the LD₅₀ of dipropyl adipate.

Comprehensive teratogenicity studies were also completed where gross, skeletal, and visceral abnormalities and fetal size were examined (Singh et al. 1973). Gross abnormalities were rarely seen with dipropyl adipate as compared other adipic acid esters. No visceral abnormalities were seen, and only one animal at the highest treatment dose displayed skeletal abnormalities (absent tail). In cross-comparative studies with their phthalate counterparts, adipates tended to yield fewer fetal deaths, fewer resorptions, and fewer skeletal abnormalities (Singh et al. 1973).

7.6.2.6 Genotoxicity

No experimental data were found. However, TOPKAT modeling predicted that DnPA would not be mutagenic at high confidence. The related chemical, DEA was reported as positive in a dominant lethal bioassay in male rodents (Singh et al. 1975).

7.6.2.7 Carcinogenicity

Experimental data not found. TOPKAT models indicate DnPA is not carcinogenic.

7.6.2.8 Neurotoxicity

No experimental data were found. DnPA is not anticipated to be a neurological hazard.

7.6.3 Ecological Data

7.6.3.1 Fate and Transport

DnPA is expected to have high mobility in groundwater due to its solubility, but it is not expected to pose a hazard to surface or drinking water due to a high tendency to adsorb to soil and other particulates, and its ready biodegradability. DnPA is expected to exist in the atmosphere primarily in particulate form due to its high aqueous solubility and low Henry's Law Constant. DnPA is not expected to bioaccumulate due to its low log K_{OW} and ready biodegradability. Environmental persistence is expected to be days to weeks.

7.6.3.2 Ecotoxicity

No data were found for DnPA across any of the aggregated or specialized literature databases. TOPKAT modeling predicts an LD₅₀ in fathead minnow of 4.8 mg/L; the prediction for Daphnia is unreasonably low and unreliable.

The ECOSAR program models DnPA as an ester, and predicts a 96-hour EC₅₀ in green algae of 3.09 mg/L, a 48-hour LC₅₀ in Daphnia of 9.0 mg/L, and a 96-hour LC₅₀ in fish of 5.00 mg/L. Data were found for DEA and DBA (ECOTOX 2009). For DEA, the 24- and 48-hour acute LC₅₀ for fathead minnow were 22.5 and 17.3 mg/L respectively. For DBA, the 96-hour LC₅₀ was 3.64 mg/L in fathead minnow (ECOTOX 2009). Further, using the EPA's EPI Suite modeling package, the log BCF for the series DEA, DnPA, and DBA are estimated to be 1.23, 1.88, and 1.15, respectively, which suggests these adipate esters will not bioaccumulate.

7.6.3.3 Degradation and Treatment

Adipate esters contain a functional group that can absorb light at >290 nm and, therefore, may undergo direct photolysis in the environment (Kim et al. 2019; NCBI 2020). DnPA is predicted to be readily biodegradable. Removal of DnPA in wastewater treatment facilities is predicted to be about 10%, primarily due to sludge adsorption.

7.7 2-Nitrodiphenylamine [2-NDPA]

7.7.1 General Information

Very little toxicological information for 2-NDPA was located; however, a toxicological profile for Otto Fuel II, a torpedo fuel for which 2-NDPA is a minor component, exists (ATSDR 1995). A primary source of information on 2-NDPA is a 1979 literature review carried out for the Army by Atlantic Research Corporation (USAMRDC 1979) (Figure 4).

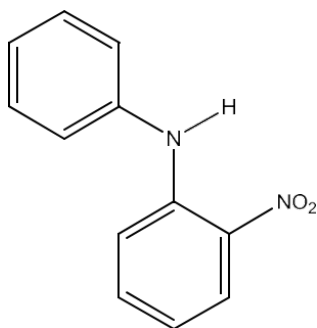


Figure 4. 2-Nitrodiphenylamine [2-NDPA]

7.7.2 Toxicology data

7.7.2.1 Oral

A rat oral LD₅₀ for 2-NDPA was reported as 6,150 mg/kg (USAMRDC 1979). The LD₅₀ for Otto Fuel II, which contains 1.5% 2-NDPA, was 2,000 mg/kg in rat; few experimental details were provided (ATSDR 1995). TOPKAT modeling predicted an acute oral LD₅₀ in rats of 979.1 mg/kg at high confidence, and a chronic LOAEL of 63.1 mg/kg-day also at high confidence.

The Army review concluded that 2-NDPA had a low acute toxicity to mammals, and that metabolism to the 4-hydroxy- and 4,4'-dihydroxy metabolites with rapid elimination from the body was likely (USAMRDC 1979). N-hydroxy-2-nitrodiphenylamine was also postulated as a metabolite based upon the appearance of methemoglobin in the blood. Exposing rats to an oral dose of 3,070 mg/kg for an unspecified time resulted in elevation of methemoglobin levels to 9.45%.

7.7.2.2 Inhalation

No experimental data were found. TOPKAT modeling predicted an inhalation LC₅₀ in rats of 1.3 g/m³-hour at high confidence. 2-NDPA is categorized as GHS hazard statement H335 – “may cause respiratory irritation” (Kim et al. 2019; NCBI 2020).

7.7.2.3 Dermal

2-NDPA is listed as a GHS Cat 2 for skin irritation (H315) (Kim et al. 2019; NCBI 2020).

7.7.2.4 Ocular

The SDS indicated that 2-NDPA was irritating to the eyes (GHS H319) (Kim et al. 2019; NCBI 2020). TOPKAT modeling predicts 2-NDPA is likely to be a mild ocular irritant.

7.7.2.5 Development and Reproduction

No experimental data were found. TOPKAT modeling predicts 2-NDPA will not be a developmental or reproductive toxicant at moderate confidence. The structurally-related 4-nitrodiphenylamine (4-NDPA) was found to induce moderate maternal toxicity in rats at doses of 1,000 mg/kg-day and high maternal toxicity at 3,000 mg/kg-day when administered on gestation days 6 through 15, with pups exhibiting reduced body weight and an increase in the number of presacral vertebrae. No developmental effects were noted in the absence of maternal toxicity (USAMRDC 1979).

2-NDPA has been screened in several high throughput bioassays. It was identified as a potential androgen receptor antagonist at 2.7 µM (Williams et al. 2017).

7.7.2.6 Genotoxicity

2-NDPA was tested in a large compound screening program (Zeiger et al. 1992). Ames tests

with *S. typhimurium* strains TA97, TA98, TA100, and TA1535 were negative for mutagenicity without microsomal activation and were negative in the presence of hamster and rat Aroclor 1254-activated microsomal fractions; the highest concentration tested was 1,000 µg/plate (~1 mg/mL) (CCRIS 2018).

7.7.2.7 Carcinogenicity

No experimental data were found. TOPKAT modeling of carcinogenicity is largely negative. A provisional peer reviewed toxicity value (PPRTV) could not be ascertained due to a lack of available data (EPA 2011).

7.7.2.8 Neurotoxicity

No experimental data were found. 2-NDPA is not anticipated to be a neurological hazard.

7.7.3 Ecological Data

7.7.3.1 Fate and transport

With an estimated water solubility of 27.6 mg/L and a log K_{OC} of 3.12, it was determined that 2-NDPA would have low to moderate mobility in groundwater, and was unlikely to pose a hazard to surface or drinking water (EPA 2013). The Henry's Law Constant of 9.07×10^{-8} atm-m³/mol indicates that 2-NDPA will only be present in the atmosphere in particulate form.

The Army study calculated a log BCF of 2.10, which was based upon an estimated log K_{OW} value of 3.07 (USAMRDC 1979). Using the same method of calculation, but with the experimentally determined log K_{OW} of 3.66 (Williams et al. 2017), the log BCF is estimated to be 2.55, which suggests 2-NDPA has a moderate potential for bioaccumulation in aquatic organisms and may be concentrated up the food chain.

7.7.3.2 Ecotoxicity

The Army study concluded that 2-NDPA was probably toxic to fish and invertebrates in the low ppm range (USAMRDC 1979). This conclusion was based upon aquatic toxicity data for compounds similar to 2-NDPA, as no toxicological data were available for 2-NDPA.

TOPKAT modeling predicts an EC_{50} in *Daphnia* of 0.487 mg/L at high confidence, and an LD_{50} in fathead minnow of 22.1 mg/L at low confidence. The ECOSAR model predicts a 96-hour EC_{50} in green algae of 5.06 mg/L, a 48-hour LC_{50} in *Daphnia* of 3.57 mg/L, and a 96-hour LC_{50} in fish of 5.38 mg/L. The structural isomer, 4-nitrodiphenylamine, is very toxic to aquatic invertebrates (*D. magna* 48 hour EC_{50} = 1.0 mg/L; GHS category I) and has potential for bioaccumulation (Organization for Economic Cooperation and Development (OECD) 1998).

7.7.3.3 Degradation and Treatment

Decomposition of 2-NDPA was observed when an aqueous solution containing both 2-NDPA and propylene glycol dinitrate (another component of Otto Fuel II) was exposed to ultraviolet

light under either air or nitrogen (Wyman et al. 1984). Under both sets of conditions, 2-NDPA was removed from the solution based upon disappearance of its characteristic peak at 442 nm; no data on its decomposition were presented. This does not necessarily indicate that 2-NDPA will be destroyed by exposure to sunlight, as ultraviolet wavelengths less than 290 nm, which are not present in sunlight due to atmospheric absorption, were not filtered out (ATSDR 1995).

EPI Suite modeling predicts 17.2% degradation of 2-NDPA in wastewater treatment plants, primarily due to sludge adsorption. Further, 2-NDPA has reportedly been degraded by mixed cultures of microorganisms in soil or sediment, when it is available as the sole carbon source (Elvey et al. 1977). However, when presented to a culture of mixed microorganisms designed to degrade recalcitrant substances in wastewater from treatment plants, there was no evidence of biodegradation of 2-NDPA based upon failure to detect any metabolites (Wyman et al. 1984). Microbial degradation does not appear to be of significant importance in the environmental fate of 2-NDPA (ATSDR 1995).

7.8 Candelilla Wax

7.8.1 General Information

Candelilla wax is obtained from candelilla plants (*Euphorbia antisiphilitica*, *Euphorbia cerifers*, or *Pedilanthus pavonis*) through extraction by immersion in a tank containing acidified boiling water and sulfuric acid. Candelilla wax is a hard and brittle wax and is comprised of about 20–29% wax esters, 12–14% alcohols and sterols, 49–50% hydrocarbons, 7–9% free acids, 2–3% moisture and 1% mineral matter.

Its chemical and physical properties vary with the age of the plant and the year in which it is collected. The wax is insoluble in water but soluble in acetone, chloroform, benzene, and other organic solvents (Rojas-Molina et al. 2013). Candelilla wax is frequently used in cosmetics in concentrations from 0.1–50% and is affirmed GRAS by the FDA (Code of Federal Regulation (CFR) 2020b).

7.8.2 Toxicology Data

Due to the variable, polymeric nature of candelilla wax, QSAR modeling is not feasible for this material.

7.8.2.1 Oral

The acute oral LD₅₀ of candelilla wax exceeds 5,000 mg/kg in rats (ACT 1984; International Programme on Chemical Safety (IPCS) 2009). Also, in a 6-month dog study and a 2-year rat study, with highest dietary levels equivalent to 600 and 750 mg/kg-day, respectively, showed no compound-related toxicity (WHO 2006a).

7.8.2.2 Inhalation

Experimental data not found; however, candelilla wax is an unlikely inhalational hazard.

7.8.2.3 Dermal

Candelilla wax and cosmetic formulations containing up to 11% candelilla wax have been tested for skin irritation and systemic toxicity (American College of Toxicology (ACT) 1984). Candelilla wax (75% in corn oil) caused minimal irritation when applied to shaved rabbit skin. No irritation was observed in rabbits when 100% candelilla wax was applied under occlusive dressings. A lipstick product containing 10.98% candelilla wax was tested in a modified Draize assay on six New Zealand white rabbits. After 72 hours, slight erythema and edema were observed in one rabbit (abraded and intact skin) and a second rabbit had well defined erythema and edema on abraded skin. As the product contained a mixture of ingredients, skin irritation was not definitively linked to the presence of candelilla wax.

A dermal toxicity test using New Zealand white rabbits was conducted for a cream containing 3.5% candelilla wax (ACT 1984). The cream (500 mg/kg) was applied five times per week for 4 weeks. No animals died during the study. Clinical chemistry and hematology data showed no differences between treated and control groups. No differences between the groups were found for all endpoints collected at necropsy (e.g., body weights, organ weights, bone marrow). Slight erythema, flaking and dry skin were observed at the application site.

Cosmetic formulations containing candelilla wax have been patch tested on human subjects (ACT 1984). Neither the single or repeated treatment patch tests were positive for irritation or sensitization.

7.8.2.4 Ocular

No ocular irritation was observed in rabbits that had 75% candelilla wax in corn oil instilled in one eye and then observed for 7 days (ACT 1984). In a separate study, a cosmetic formulation containing 10.98% was found to be non-irritating over a 72-hour observation period when applied to rabbit eyes (ACT 1984).

7.8.2.5 Reproduction and Development

A cream formulation containing 3.5% candelilla wax was tested for teratogenicity and embryotoxicity in rats (ACT 1984). A 2,000 mg/kg-day dose (=70 mg/kg-day candelilla wax) was applied to clipped skin from gestation day 6-16; untreated pregnant rats served as controls. Nine of the 12 treated rats had slight to moderate desquamation at the test site. Endpoints for developmental effects (e.g., corpora lutea, implantation sites, fetuses, resorption sites, sex ratios, fetal length and weights) were all normal; no developmental toxicity was observed in this test.

7.8.2.6 Genotoxicity

Candelilla wax was not mutagenic in the Ames test *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and in *E. coli* strain WP2, either with or without S9 activation (CCRIS 2018).

7.8.2.7 Carcinogenicity

In black agouti (C57) mice fed a diet containing a mixture of gum base that was 25% candelilla wax for 12–13 months, at doses as high as 7,500 mg/kg-day, the candelilla wax mixture was noncarcinogenic. Sprague-Dawley rats fed up to 7,500 mg/kg-day of a gum base containing 25% candelilla wax showed no signs of carcinogenicity that was any different from the controls (IPCS 2009).

7.8.2.8 Neurotoxicity

Experimental data not found. Candelilla wax is not anticipated to be a neurological hazard.

7.8.3 Ecological Data

7.8.3.1 Fate and Transport

Due to its insolubility in aqueous media and waxy nature, candelilla wax is not expected to pose a transport hazard in either water or soil. Being a nonvolatile substance, candelilla wax is likely to be found in the atmosphere only in a particulate form. Candelilla wax is unlikely to bioaccumulate since its insoluble nature will not make it bioavailable.

7.8.3.2 Ecotoxicity

Experimental data not found. Candelilla wax is a natural product from plants and is not expected to be an ecotoxicity hazard.

7.8.3.3 Degradation and Treatment

Experimental data not found. Candelilla wax is likely to degrade slowly in the environment.

7.9 Carbon Black [C]

7.9.1 General Information

Carbon black is a generic term for a particulate form of elemental carbon that is manufactured by gas phase pyrolysis and partial combustion of hydrocarbons. Carbon blacks are categorized on the basis of the different combustion processes by which they are made, such as acetylene black, channel black, furnace black, lamp black, or thermal black (Kim et al. 2019; NCBI 2020).

A large number of epidemiological studies of carbon black workers have been conducted. Non-cancer respiratory effects in carbon black workers have been reported to include cough, sputum production, bronchitis, chest radiographic opacities (e.g., pneumoconiosis) and decrements in lung function (Kim et al. 2019; NCBI 2020).

Most toxicological information available for carbon reflect concern with the possibility of carcinogenicity associated with respiration of inhalable carbon particles. However, limited amounts of non-inhalation data are available for various forms of carbon.

7.9.2 Toxicology Data

7.9.2.1 Oral

The LD₅₀ for rats orally exposed to carbon black has been determined to be >15,400 mg/kg and >3000 mg/kg in rabbits (Gandhi 2005). Carbon is considered essentially non-toxic to humans via the oral route, with a lethal dose >15 g/kg (Kim et al. 2019; NCBI 2020).

Female Sprague-Dawley rats and female CF1 mice treated with 1, 2-dimethylhydrazine to induce colonic adenocarcinoma were fed carbon black at 2.05 g/kg for 52 weeks. No differences in tumor incidences were seen in rats or mice (Pence and Buddingh 1985). Although exact amounts were not reported, no effects of a dietary exposure to 10% carbon black in mice for 72 weeks were observed (Nau et al. 1976).

No differences in tumor incidence were observed in a 2-year feeding study with 2.05 g/kg carbon black in female Sprague-Dawley rats and female CF1 mice (Pence and Buddingh 1985).

7.9.2.2 Inhalation

Hamsters exposed to 3 mg/ft³ carbon black for 172 days failed to display any observable changes in the pathology of the larynx, trachea, hypopharynx, or cervical esophagus compared to controls (Nau et al. 1976). However, exposure to 1.5 mg/ft³ resulted in edema in the subepithelial area of the thyroarytenoid fold and retention of amorphous eosinophilic material in the subglottic glands.

In the same study, Rhesus monkeys were exposed to 1.5 mg/ft³ for 160 days, and failed to display any impaired pulmonary function, but did accumulate carbon black particles in the primary lymphatic system that surround the bronchiolar areas (Nau et al. 1976). Exposed animals experienced destruction of the alveolar walls in the bronchioles and parenchyma surrounding the pulmonary veins.

Carbon black is considered to be a non-specific irritant with toxic effects similar to other insoluble particles (Gandhi 2005). Few toxicity data exist for acute inhalation exposure to carbon black due to concern over the potential for cancer from longer term exposures (Driscoll et al. 1996; Heinrich et al. 1994). A description of the current views on the mechanism of inhalation carcinogenicity is discussed below. Long-term inhalation of carbon black particles can result in changes in the human lung typical of pneumoconiosis or changes expected to become pneumoconiosis in the future. Hence, pneumoconiosis has been identified as an occupational disease of workers exposed to carbon black production and use (Kim et al. 2019; NCBI 2020).

7.9.2.3 Dermal

Dermal carcinogenicity was evaluated in groups of male C3H/HeJ mice receiving 25 µL volumes of various types of carbon fibers that were suspended in benzene and applied to the skin of the back three times per week until death, beginning at age 51 to 76 days (Kim et al. 2019; NCBI 2020). The mean survival time of the treated groups exceeded that seen for the control group.

7.9.2.4 Ocular

Carbon black is used as a pigment in liquid eye liners and mascaras. When used over a period of 2 years, application of carbon black-containing products has resulted in black pigmentation of the eyelid and although there is lymphocytic filtration and uptake of the pigment by macrophages, deposits cause essentially no symptoms (Kim et al. 2019; NCBI 2020).

As graphite, a dust irritation is possible, resulting in conjunctivitis epithelial hyperplasia of the cornea and eczematous inflammation of the eyelids (Kim et al. 2019; NCBI 2020).

7.9.2.5 Reproduction and Development

The reproductive and developmental toxicity of carbon-containing nanoparticles, to include carbon black nanoparticles (Printex-90) have been investigated. Most studies investigate the effects from respiratory exposure to carbon nanoparticles and are limited due to either few endpoints or single dose treatment regimens. Thirteen-week-old offspring from mice exposed to 2 mg/kg Printex-90 via instillation on gestation days 5 and 9 had increases in markers for kidney fibrosis (Umezawa et al. 2011). In a separate study, a systemic inflammatory response was observed in postnatal day (PND) 1–5 pups of mice gestationally exposed (days 9 and 15; intranasal instillation) to 0.095 mg/kg carbon black nanoparticles (El-Sayed et al. 2015). A review of the reproductive-developmental toxicity of carbon black, highlighted the weaknesses of the aforementioned, and similar studies and concluded that the weight of evidence for carbon black as a reproductive/ developmental toxicant was inadequate (Chaudhuri et al. 2018).

7.9.2.6 Genotoxicity

Carbon tested positive in the Sister Chromatid Exchange (SCE) test (Kim et al. 2019; NCBI 2020). Carbon nanotubes, an allotrope of carbon, tested negative in Chinese Hamster V79 fibroblast cells and in the Ames test either with or without S9 activation (Kim et al. 2019; NCBI 2020).

7.9.2.7 Carcinogenicity

There is sufficient evidence in animals, but insufficient human evidence of the carcinogenicity of carbon black. Overall, carbon black is classified as possibly carcinogenic to humans (Group 2B) (Kim et al. 2019; NCBI 2020).

Some carbon black products contained very strongly adsorbed 3,4-benzpyrene, a carcinogenic hydrocarbon, as an impurity. Some European carbon blacks contained up to 1% 3,4-benzpyrene by weight, while U.S. manufactured carbon black had significantly less than this (Kim et al. 2019; NCBI 2020). The IARC's reclassification of carbon black from group 3 to group 2B was reviewed (Valberg et al. 2006). The elucidated mechanism for carcinogenicity reveals that the particulate exposures result in macrophage activation of various signaling pathways that amplify inflammation (IARC 1996).

Mutations and fibrosis result from a chronic inflammatory state that promote metaplastic

changes and lung tumors (Knappen et al. 2004). The carcinogenic properties are therefore similar to any poorly-soluble particle: toxicity results from particle overload more than the chemistry of the molecule of interest. In light of emerging mechanistic data for the potential carcinogenicity of carbon black, current thinking holds that there is inadequate evidence of cancer risk in humans and limited evidence in experimental animals (Valberg et al. 2006).

7.9.2.8 Neurotoxicity

Data for bulk carbon black neurotoxicity was not found; however, engineered carbon black nanoparticles have been evaluated for neurotoxicity. There is some evidence in mice that reactive oxygen species (ROS) are generated in the olfactory bulb after intranasal exposure to CB-nanoparticles (Win-Shwe and Fujimaki 2011). Developmental neurotoxicity was reported in offspring from Printex-90 gestationally exposed (inhalation) mice (Umezawa et al. 2018). In this study, enlarged lysosomal granules in brain perivascular macrophages and markers for astrogliosis were observed. The extrapolation of nanoparticle toxicity data to bulk carbon black toxicity is challenging. Based on the intrinsic properties of nanoparticles, it is estimated that bulk carbon black would be less toxic than carbon black nanoparticles.

7.9.3 Ecological Data

7.9.3.1 Fate and Transport

Inorganic carbon is hydrophobic, and hence would be insoluble in aqueous systems. It will collect in sediment when wetted or adsorbed to other materials in solution. Carbon is harmless when orally consumed by fishes or mammals. Combustion of carbon will produce carbon dioxide, which is a normal product of respiration.

7.9.3.2 Ecotoxicity

Ecotoxicology data were available for the common carp (*Cyprinus carpio*) using activated charcoal. Activated charcoal is used in many aquatic filtering systems; however, effects to the fry in a slurry had not yet been tested. No adverse effects were found (Kaviraj and Das 1995). An inhalation study conducted with carbon fibers using Northern Bobwhite quail (*Colinus virginianus*) failed to provoke any adverse effects, whereas exposure to high concentrations of the carbon fibers did (Driver, C., pers. comm.). The ECOSAR program predicts a 96-hour EC₅₀ in green algae of 96 mg/L, a 48-hour LC₅₀ in Daphnia of 170 mg/L, a 96-hour LC₅₀ in fish of 170 mg/L, and a 14-day earthworm LC₅₀ of 240 mg/L based upon dry soil.

7.9.3.3 Degradation and Treatment

Inorganic carbon is not of concern from an environment perspective and does not require special treatment in this regard.

7.10 Elemental Lead [Pb] (A Component of LC-12-15)

7.10.1 General Information

Lead is used in an array of commercial applications and is found in many industrial and commercially available products. These include the manufacture of storage batteries, lead alloys that are used in bearings, brass and bronze alloys, and some solder formulations. Lead is also used commercially in sheets and pipe for nuclear and x-ray shielding, cable coverings, noise control materials, chemical resistant linings, Military applications including ammunition, and in pigments and lead compounds that are used in glass making, ceramic glazes, plastic stabilizers, caulk, and paints.

The general population may be exposed to lead in ambient air, foods, drinking water, soil, and dust. Segments of the general population at highest risk of health effects from lead exposure are preschool-age children and pregnant women and their fetuses. Within these groups, relationships have been established between lead exposure and adverse health effects. Other segments of the general population at high risk include individuals living near sites where lead was produced or disposed.

Lead is a recognized occupational health hazard. Lead adversely affects many biochemical and biological processes such as hematopoietic, neurological, metabolic endpoints, and behavioral outcomes, especially in exposed children. The effects of lead on the hematopoietic system markedly suppress hemoglobin synthesis. Additionally, anemia was observed in children at blood concentrations that exceeded 1.92 $\mu\text{mol/L}$ (40 $\mu\text{g/dL}$), and increased lead exposure is associated with neuro-psychiatric disorders including attention deficit hyperactivity disorder (ADHD), anti-social tendencies, reduced intelligence quotient, and academic deficits. Impaired psychological and neurobehavioral functions have also been found after long-term lead exposure in workers (Kim et al. 2019; NCBI 2020).

7.10.2 Toxicology Data

7.10.2.1 Oral

The LD_{50} of lead depends on its speciation. Ingestion and exposure to stomach acid may result in the liberation of lead cations. Alternatively, food in the stomach may limit the bioavailability of lead. Absorption of lead ions occurs predominately in the small intestine. To represent a soluble form of lead, lead acetate was selected. The reported human oral LD_{Lo} is 714 mg/kg for lead acetate (NIOSH 2019a).

Sufficient human data exist to describe chronic effects of lead exposure. The ATSDR updated and revised its toxicological profile for lead and it should be consulted for a thorough review (ATSDR 2020c). Key chronic effects identified in the ATSDR profile by target organ/system include respiratory, cardiovascular (hypertension), and hematological (heme synthesis) systems. Adverse effects are found at chronic blood lead levels (BLL) of $<10 \mu\text{g/dL}$.

7.10.2.2 Inhalation

Toxicological effects from inhaled lead particles or dust have been known since the initial published reports of lead toxicity following inhalation exposures (Cooper 1947; Cotter 1946). One of the seminal studies in this area reported on an apparent epidemic of lead poisoning in children by inhalation and of the first observations of the characteristic skeletal changes that are now known to be involved (Cooper 1947). Furthermore, occupational exposure to lead occurs for workers in the lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops, and other industries requiring flame soldering of lead solder. A major route of lead exposure in these occupations is inhalation of lead-bearing dusts and fumes. Particle size affects the distribution and fate of inhaled lead particles. Lead particles that reach the alveoli are absorbed by phagocytosis or transported across capillary walls; larger particles that deposit in the upper airways encounter mucociliary clearance and are subsequently ingested (Neal and Guilarte 2013).

Very few animal model studies are available for an assessment of the inhalational exposure to lead. However, the available studies have provided insights into the biological and toxicological health effects of inhalational exposures to lead (Bingham et al. 1968; Bizarro et al. 2003). In one study, a decreased number of alveolar macrophages was found in the bronchoalveolar lavage fluid (BALF) obtained from the lungs of rats that had inhaled small particles of lead sesquioxide (Pb_2O_3) for 3 to 12 months, as compared with control animals exposed to filtered air (Bingham et al. 1968). In this study, young adult male and female rats were exposed continuously for 24 hours per day to a lead aerosol for periods up to 1 year. It was pointed out in this report that the concentrations of lead particles to which the animals in both dosing test groups were exposed (i.e., 10 and 150 $\mu g/m^3$) were particularly significant in that they were within the range encountered in certain environmental situations at that time (Bingham et al. 1968). In the second study, CD-1 male mice exposed to 0.01 M lead acetate intermittently for 4 weeks showed a time-related increase in the fraction of damaged mitochondria in Sertoli cells, which according to study investigators might provoke a transformation and interference in spermatogenesis (Bizarro et al. 2003).

7.10.2.3 Dermal

Dermal absorption of inorganic lead powder through unabraded human skin is considered to be minimal (WHO 2006b). Skin deposition of lead dust is a concern for workers exposed to lead due to the potential for hand to mouth transfer of lead dust, especially if individuals eat and/or drink near the lead source. A health hazard evaluation was conducted by NIOSH at a Missouri bullet manufacturing facility (Jackson et al. 2018). It was determined that dermal deposition of lead dust, skin lesions from molten lead, dry sweeping of the floors, and poor hand and food/drink hygiene practices resulted in lead exposure as measured by elevated BLL in the employees. Dermal adsorption of lead salts was considered a contributing factor to the elevated BLL.

7.10.2.4 Ocular

Using a rat model for ocular effects from gestational lead exposure (GLE), female Long-Evans

hooded rats were given drinking water containing lead at 0, 27, 55, or 109 ppm from 2 weeks prior to mating, then throughout gestation through PND 10 (Fox et al. 2008). Investigators studied a range of maternal and litter indices, BLL, retinal lead concentrations, zinc levels, and body weights. At PND 90, offspring were further evaluated for retinal effects. In PNDs 0–10 offspring, peak BLL were < 1, 12, 24, and 46 µg/dL from exposure to 0, 27, 55 and 109 ppm, respectively. These BLL were comparable to and exceeded action level lead concentrations in children exposed to high lead. Further, vision changes have been reported in people exposed to these levels of lead. In the PND 90 offspring, compared to controls, rats in the 27 and 55 ppm dose groups had increased numbers of rod cells and neurogenesis, while at the highest level tested 109 ppm, rod selective toxicity was observed.

Additional studies of the potential ocular toxicity that might be provoked by lead exposure have also been derived from alternative and *in vitro* tests of toxicity. For example, *in vitro* studies using rat retinas that were incubated in the presence of calcium or lead showed increased high molecular weight DNA fragmentation and a higher number of apoptotic rods. In addition, retinal mitochondrial ATP synthesis was decreased, mitochondrial cytochrome C was released, and caspase activity was increased. These effects were additive in the presence of physiological concentrations of both calcium and lead (WHO 2006b). Further, *in vitro* studies suggest that rod cells are more sensitive to the effects of lead than cone cells (Bingham et al. 2001).

7.10.2.5 Development and Reproduction

In a study relevant to military service personnel in Iraq, a lead-alloy powder that was used in Iraq in the manufacture of grids for storage battery electrodes was tested for its putative health effects on the reproduction capabilities of male BALB/c mice (al-Hakkak et al. 1988). This study examined two lead concentrations (25 and 50 mg/kg chow) that were fed to male mice for 35 or 70 days starting at the time of weaning. A subset of the males were mated individually to two untreated females and the results showed a significant increase in post-implantation losses of embryos in utero and a significant decrease in litter size of surviving pregnancies. Light microscopic examination showed a general trend towards reduced spermatogenic activity (al-Hakkak et al. 1988).

In numerous studies, the reproductive toxicology and growth effects from lead exposure in developing mammals were determined. Rats were exposed to 0.6% lead acetate in drinking water *in utero*, and during the pre- and post-pubertal periods (Ronis et al. 1996). In male rats, testicular weights and all secondary sex organs were significantly decreased in those animals that were exposed during the pre-pubertal period. Further, serum testosterone levels were significantly suppressed, and most severely so in animals that were exposed *in utero*. In female rats exposed during the pre-pubertal period, delayed vaginal opening and disrupted estrous cycling was observed in approximately half of the animals. The group treated *in utero* displayed suppressed levels of circulating estradiol that was accompanied by significant decreases in both circulating luteinizing hormone (LH) concentrations and pituitary LH protein concentrations. These findings suggested a dual site of action from lead exposure: (a) at the level of the hypothalamic pituitary axis; and (b) at the level of gonadal steroid biosynthesis. Comparable hormonal effects have been observed in female monkeys at BLL of 35 µg/dL (WHO 2006b). It has also been shown that when both parents were exposed to lead, reduced numbers of rat and mouse offspring were observed (Bingham et al. 2001). The effects were classified as

“gametotoxic,” which were likely irreversible, intrauterine effects that were presumed to be due to lead uptake by the conceptus, and extrauterine effects due to passage of lead from the dam to nursing pups that added to the gametotoxic and intrauterine effects (Bingham et al. 2001).

Rats, prior to mating, were exposed to lead for 150 days followed by a 50-day lead-free ‘wash out’ period. It was found there was a substantial mobilization of lead from the mother to the developing fetus. Using radiotracer lead (^{210}Pb) in female mice showed that there was also a major transfer of lead to the pup during lactation as well. The concomitant decrease in maternal bone lead content supported the working hypothesis that bone resorption of lead occurs during lactation (WHO 2006b).

Rats were chronically exposed to low concentrations of lead at different stages of development, and tested with respect to active-avoidance learning and hippocampal long-term potentiation. When exposure comprised the prenatal and the early postnatal periods and was continued into adulthood, both processes were impaired. However, when exposure started at 16 days after birth, neither learning nor hippocampal potentiation was affected (WHO 2006b). In complementary studies, neurochemical parameters were measured in discrete areas of the brain of rat pups whose mothers were intoxicated with lead in the drinking-water (at a dose of 300 ppm) from day 1 of pregnancy until PND 12 (WHO 2006b). This treatment significantly reduced the activity of alkaline phosphatase and ATPase in the brain and reduced the concentration of adenine nucleotides, most notably in the striatum, but not in the hypothalamus. Exposure to lead via the drinking water also reduced the concentration of neurotransmitters throughout the brain, especially in the hippocampus (WHO 2006b).

In a comprehensive study of the developmental and reproductive effects of lead, female C57Bl/6 mice were exposed to water containing 0, 27 (low), 55 (moderate), or 109 ppm (high) of lead from 2 weeks prior to mating, throughout gestation, and until PND 10 (Leasure et al. 2008). Maternal and litter measures, BLL, and body weights were determined during the course of the entire study. Locomotor behavior in the absence and presence of amphetamine, running wheel activity, rotarod test, and dopamine utilization were examined in 1-year-old mice. Peak BLL were respectively <1 , ≤ 10 , 24–27, and 33–42 $\mu\text{g/dL}$ in control, low-, moderate-, and high-dose GLE groups at PND 0–10 (Leasure et al. 2008). One-year-old male but not female GLE mice exhibited late-onset obesity. Similarly, 1-year-old male GLE mice displayed decreased spontaneous motor activity, increased amphetamine-induced motor activity, and decreased rotarod performance. Dopamine levels and its major metabolite were altered in 1-year-old male mice, although only forebrain utilization increased. Further, GLE-induced alterations were consistently higher in low-dose treated GLE mice (Leasure et al. 2008).

In a study conducted in squirrel monkeys (Logdberg et al. 1987), 11 pregnant animals were orally exposed to lead during the latter two-thirds of pregnancy resulting in a mean BLL concentration of 0.54 $\mu\text{g/mL}$ (2.61 $\mu\text{mol/L}$), with a range of 0.39–0.82 $\mu\text{g/mL}$ (1.88–3.96 $\mu\text{mol/L}$), at a dosing regimen that failed to elicit any maternal toxic symptoms. Some offspring had lesions that were similar to lead encephalopathy and growth retardation of the fetal cerebrum, and neurological and behavioral symptoms that were evident at the adult age of these animals. Lead levels in the cerebral tissue of the offspring (to include an abortion, stillborn, a sacrificed full-term fetus, and a neonatal death) were between 0.1–0.7 $\mu\text{g/g}$. There was an increase in prematurity and pre- and perinatal mortality, and there was a reduction in the size of the

offspring at birth. Further, the head circumference tended to be reduced at the post-natal stage of development (Logdberg et al. 1987).

7.10.2.6 Genotoxicity

The genotoxicity of lead compounds has been extensively studied. Mutagenicity assays of lead compounds in prokaryotic organisms have mostly yielded negative results. Studies assessed gene mutation and DNA damage in *S. typhimurium*, *Escherichia coli*, and *Bacillus subtilis* and gene conversion and mitotic recombination in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation (WHO 2006b). Only lead bromide has induced gene mutations in *S. typhimurium* and *E. coli* and it was likely that the bromine ion contributed to the effect (WHO 2006b).

DNA damage as single stranded breaks in genomic DNA as observed by comet assays, was noted in a variety of organ systems, bone marrow hematopoietic cells, peripheral blood leukocytes, and spermatozoa of mice and rats on repeated inhalation or oral exposures to lead or lead acetate (ATSDR 2020b). In addition, disseminated hypomethylation in rat hepatic DNA was seen following a single intravenous infection of lead nitrate. The observed hypomethylation was associated with increased cellular proliferation. Exposure to lead compounds was correlated with increased DNA synthesis and hepatic cellular proliferation following intravenous injection.

Similarly, studies have reported chromosomal damage on exposure to lead compounds (ATSDR 2020b; WHO 2006b). Chromosomal aberrations were seen in bone marrow cells and spermatocytes in rat and mouse models following single or repeated exposure to the test article by IP, dietary or oral gavage delivery. However, increases in the frequency of chromosomal aberrations failed to consistently show any dose-dependent effects. Exposure to lead compounds has been associated with SCEs in the bone marrow of mice and rats following intravenous exposure. Studies assessing lead compounds for micronucleus (MN) formation in bone marrow erythrocytes of rats and mice were positive following multiple exposure routes (i.e., oral gavage, drinking water, and IP delivery) of the test article.

There is evidence for lead-induced DNA damage in workers exposed to lead (ATSDR 2020b; WHO 2006b). For example, lead smelter workers with BLL of 24.8 ± 14.7 µg/dL had a significant increase in the percent of leukocytes with DNA damage. Multiple studies have found increased micronuclei in blood lymphocytes of exposed workers. The presence of co-exposures in workers should be considered, as a strong correlation to smoking was identified and could contribute to genotoxicity (ATSDR 2020b).

7.10.2.7 Carcinogenicity

There is sufficient evidence in experimental animals for the carcinogenicity of lead acetate, lead subacetate, lead chromate, and lead phosphate (Kim et al. 2019; NCBI 2020). However, there is inadequate testing in experimental animals for the carcinogenicity of lead oxide and lead arsenate, and there is inadequate evidence in experimental animals supporting the carcinogenicity of lead powder (elemental lead). Thus, a weight of evidence evaluation classifies inorganic lead compounds as B2; probable human carcinogens (WHO 2006b). It has been

proposed that lead and lead compounds are anticipated to be human carcinogens based on the limited available evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from available work conducted in experimental animals (ATSDR 2020b).

In experimental animals, the kidney is a consistent target organ for lead induced cancer. In rats, chronic exposure to 5.0 mg lead/L in drinking water provoked renal effects (WHO 2006b). The median blood lead concentration in these treated rats was 11 µg/dL. At this concentration, cytomegaly and karyomegaly in renal proximal tubular cells of the kidney were observed. Proximal tubular cells from rats exposed to 50 and 250 ppm for 6 or 9 months showed intranuclear inclusion bodies and mitochondrial swelling only in the rats treated for 9 months (WHO 2006b). In similar work, rats chronically treated with lead demonstrated nephropathy and subsequently developed renal tumors, adenomas, and adenocarcinomas. Moreover, chronic exposure of rats to high doses of lead in the diet subsequently developed chronic cystic nephritis after approximately 6 months of treatment (Bingham et al. 2001).

In *in vitro* genotoxicity experiments, several lead salts and lead oxide were tested and an indirect mechanism for DNA damage was identified that supports the hypothesis of lead acting as a cancer promoter (Zelikoff et al. 1988).

7.10.2.8 Neurotoxicity

Lead neurotoxicity is well-described and studied. In one study, subchronic and pre-chronic lead exposure (in the form of lead acetate) in rats sought to determine the extent to which post-natal lead exposure might adversely affect both the survival and expression of neuronal neurotrophin receptors in the CNS (Kidd et al. 2008).

Neurotoxicity, impaired learning and memory capabilities have been reported in rats with BLL of 0.72–0.96 µmol/L (15–20 µg/dL) and in non-human primates at BLL not exceeding 0.72 µmol/L (15 µg/dL). Furthermore, visual and auditory impairments have been reported in experimental animal studies (WHO 2006b).

Acute neuropathological changes seen in children dying of acute lead encephalopathy were reproduced in a relevant animal model following the administration of high lead doses to suckling rats (Bingham et al. 2001). Pathological changes included brain swelling with associated brain stem herniation, compression of the ventricles, and petechial hemorrhages, especially in the white matter of the cerebellum. The primary lesion was thought to be increased permeability of the blood-brain barrier due to lead-induced changes in the capillary endothelium, which resulted in microvascular thrombosis and an associated protein-rich transudation (discharge) to the extravascular space. There was also some glial cell proliferation. Further studies with the immature rat model showed decreased mitotic activity in the external layer of the cerebellum and reduced synaptogenesis in the molecular layer cerebellum. Reduced hippocampal axonal and dendritic development was also found. The resulting dysplastic hippocampal development was associated with behavioral alterations in this animal model (Bingham et al. 2001).

In a non-human primate animal model study, visual acuity was altered in infant Rhesus monkeys that were orally dosed with lead between PNDs 5 and 365, and with observed BLL of

approximately 84 µg/dL (peak BLL between 137 and 300 µg/dL). Significant impairment of scotopic vision (vision in dim light with dark-adapted eyes) was observed only in the animals that had been treated with the highest levels of lead exposure (Bingham et al. 2001).

Experimental studies using animal models have demonstrated that lead impairs learning and memory functions at virtually all stages of the life cycle (Bingham et al. 2001). It is thought that the most susceptible period may be during the prenatal and early neonatal periods when the blood-brain barrier is not completely formed. Exposure of rats to high lead levels produces lead-protein complexes or nuclear inclusion bodies in CNS glial cells, which may be protective of the neurological effects of lead. Rat pups readily develop lead encephalopathy during the first few days of life, and resistance to lead-induced neurotoxicity occurs at 18–20 days of age. Development of resistance to lead-induced encephalopathy was also related to lead-protein complex formation in astrocytes that sequestered lead away from lead-sensitive organelles such as the mitochondria (Bingham et al. 2001). It was also found that lead exposure in older rats results in higher levels of brain lead than the same level of exposure in adult or younger rats. The older animals also experienced an increased incidence of morbidity and mortality relative to their nontreated counterparts. The most significant experimental studies have concerned impaired learning and memory functions in experimental animals with BLL below 30 µg/dL during early life as a consequence of prenatal or neonatal exposure (Bingham et al. 2001).

7.10.3 Ecological Data

7.10.3.1 Fate and Transport

Lead is an environmentally ubiquitous element, predominantly as a result of anthropogenic activities, and there is a relatively high potential risk of human exposure and environmental exposure by many diverse ecologically important mammalian, avian, aquatic, and plant organisms. In the ambient atmosphere, particulate lead is removed by rainfall or gravitational settling (e.g., wet or dry deposition). Approximately 40–70% of the deposition of lead is by wet fallout; 20–60% of particulate lead once emitted from automobiles is deposited near the source.

An important factor in determining the atmospheric transport of lead is particle size distribution. Large particles, particularly those with aerodynamic diameters of >2 µm, settle out of the atmosphere fairly rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway for those size particles emitted in motor vehicle exhaust in the past); smaller particles may be transported thousands of kilometers. The dry deposition velocity for lead particles with aerodynamic diameters of 0.06–2.0 µm was estimated to range between 0.2 and 0.5 cm/second in a coniferous forest in Sweden, with an overall particle-size weighted dry deposition velocity of 0.41 cm/second (Lannefors et al. 1983). However, the use of an average net deposition velocity of 0.6 cm/second and an average atmospheric residence time of 10 days has been recommended by the National Academy of Sciences (National Research Council (NRC) 1980).

Lead has been identified in a variety of environmental media (ambient air, surface water, groundwater, surface soil, and sediment) collected at 1,272 of the 1,684 current and former NPL hazardous waste sites (ATSDR 2020a). Lead compound solubility in water is defined by pH, water hardness, relative salinity (dissolved salt content) and presence of humic material. The

solubility of lead is highest in soft, acidic water. Equilibrium calculations show that at pH >5.4 the total solubility of lead is approximately 30 µg/L in hard water and approximately 500 µg/L in soft water (ATSDR 2020b). The environmental sink for lead is the soil and sediment. Further, because lead is strongly adsorbed to soil, it is generally retained in the upper layers of the soil and displays a minimal capacity for leaching into the subsoil and groundwater.

In addition, lead compounds may be transformed in the environment to other lead compounds; however, since lead is an element it is resistant to destruction. It should be noted that many anthropogenic sources of lead, most notably leaded gasoline, lead-based paint, and lead solder in food cans, lead-arsenate pesticides, and shot and sinkers used in hunting and fishing activities, have been eliminated or strictly regulated due to the reported environmental persistence and extensively reported toxicity of lead. Since lead is an element, it does not degrade; these former uses leave their legacy as higher environmental levels of lead.

7.10.3.2 Ecotoxicity

While the majority of lead releases are to land, they constitute much lower exposure risks than releases to air and water. Although plants and animals may bioaccumulate lead, it is not biomagnified in the aquatic or terrestrial food chain (ATSDR 2020b).

In general, the highest lead concentrations are found in aquatic and terrestrial organisms with habitats near lead mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting and fishing (i.e., lead from spent shot or sinkers); and in urban and industrialized areas. Lead may be present on plant surfaces as a result of atmospheric deposition; its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of lead in soil to plants is limited because of the strong adsorption of lead to soil organic matter, the bioavailability increases as the pH and the organic matter content of the soil are reduced. Plants grown in lead-contaminated soils were shown to accumulate low levels of lead in the edible portions of the plant from adherence of dusts and translocation into the tissues (Finster et al. 2004).

Lead may be taken up in edible plants from the soil via the root system, by direct foliar uptake and translocation within the plant, and by surface deposition of particulate matter. The amount of lead in soil that is bioavailable to a vegetable plant depends on factors including cation exchange capacity, pH, amount of organic matter present, soil moisture content, and type of amendments added to the soil. Background agricultural soil lead concentrations for major growing areas of the United States have been determined (Holmgren et al. 1993).

Uptake of lead in animals may occur as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. However, lead is not biomagnified in aquatic or terrestrial food chains. Older organisms tend to contain the greatest body burdens of lead. In aquatic organisms, lead concentrations are usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). Exposure of a fresh-water fish to several sublethal concentrations of lead for a period of 30 days showed significant accumulation of lead in the blood and tissues. The lead accumulation in tissues was found to increase with lead in water up to a concentration of 5 mg/L. At concentrations of 10 and 20 mg/L, the lead

accumulation in the tissues, although indicating an increase, was not proportional to the lead concentration in water (Tulasi et al. 1992).

It should be noted that biomagnification of organolead compounds has not been found to occur. Depuration (freeing from impurities) is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl lead. Tetraalkyl lead compounds are more toxic than trialkyl lead compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988).

7.10.3.3 Degradation and Treatment

Information available regarding the chemistry of lead in air is limited. In the atmosphere, lead exists primarily in the form of PbSO_4 and PbCO_3 . It is unclear how the chemical composition of lead changes during dispersion (ATSDR 2020c).

Tetraalkyl lead compounds, once added to gasoline, are no longer present in significant quantities in the air. However, their degradation products are still present. Based on the vapor pressure of tetraethyl lead (0.26 mmHg at 25°C) and tetramethyl lead (26.0 mmHg at 20°C), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). On sunlight exposure, tetraalkyl lead compounds decompose rapidly to trialkyl and dialkyl lead compounds, then to inorganic lead oxides by the combined action of direct photolysis, reaction with hydroxyl radicals, and ozone.

The chemistry of lead in aqueous solution is highly complex due to complex speciation. Lead has a tendency to form compounds of low solubility with the major anions found in natural waters. The amount of lead dissolved in surface waters is dependent on the pH and the dissolved salt content of the water. The maximum solubility of lead in hard water is approximately 30 µg/L at pH>5.4 and the maximum solubility of lead in soft water is approximately 500 µg/L at pH>5.4 (ATSDR 2020c). In addition, in the environment, the divalent form (Pb^{2+}) is the stable ionic species of lead. It should be noted that at pH<5.4, the formation of lead sulfate limits the concentration of soluble lead in water, while at pH>5.4, the formation of lead carbonates limits the amount of soluble lead (Callahan et al. 1979).

Naturally occurring mineral forms of lead are minor constituents in soils and sediments. Anthropogenic forms of lead (e.g., PbSO_4 , PbCO_3 , PbS , Pb(OH)_2 , PbCrO_4 , and PbClBr) are transformed by chemical and microbiological processes and will bind to soil based on pH, mineralogy, and other soil properties (Chaney et al. 1988). In freshwater and estuarine environments, sedimentation of lead bound to charged particles is an important process for the removal of lead from the water column. In wet conditions, organic lead compounds, such as tetraethyl lead and tetramethyl lead, are subject to photolysis and volatilization. The degradation products evolve from trialkyl to dialkyl species, and eventually to inorganic lead oxides (Chaney et al. 1988). The degradation products may include trialkyl lead carbonates, hydroxides, and halides. These products are known to be environmentally more persistent than the original tetraalkyl lead compounds. Atmospheric lead species will undergo wet and/or dry deposition to soils; the ultimate fate and speciation of lead compounds is based on their molecular composition, volatility, sensitivity to photolysis, oxidative processes and soil conditions (ATSDR 2020c).

7.11 Copper Compounds [Cu] (A Component of LC-12-15)

7.11.1 General Information

Copper is an essential trace element, but ingestion of large amounts can result in toxicity. The normal daily intake of copper for adult humans is 0.9–2.2 mg. Copper is mainly absorbed through the gastrointestinal tract. The toxicity of copper, when it exceeds homeostatic control, is derived from its effects on the structure and function of biomolecules such as DNA, membranes, and protein directly or through oxygen-radical mechanisms (Kim et al. 2019; NCBI 2020).

7.11.2 Toxicology Data

No major toxicological distinctions are seen between the +1 and +2 valence states of copper. Chronic copper toxicosis has been found only in patients with Wilson's disease (Kim et al. 2019; NCBI 2020).

7.11.2.1 Oral

Oral toxicity of copper compounds varies greatly with species and solubility of the copper compound. The LD₅₀ for copper acetate is 501 mg/kg in rat, 196 mg/kg in mouse and 250 mg/kg in rabbit (Kim et al. 2019; NCBI 2020). Generally, toxicity increases with solubility. Death is preceded by gastric hemorrhage, tachycardia, hypotension, hemolytic crisis, convulsions, and paralysis. Adverse health effects are also noted in cases of copper deficiency, to include anemia, neutropenia, and bone abnormalities; the mean daily intake of copper in human adults is between 0.9 and 2.2 mg/day. (Kim et al. 2019; NCBI 2020). The lowest published toxic dose in human is 0.01 mg/kg (NIOSH 2019a).

Fisher rats given 150–600 ppm copper chloride in feed for 60 days had changes in clinical chemistry endpoints (glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT)) (Sugawara et al. 1995). At 600 ppm, hepatic clearance of copper was impaired indicating copper overload.

7.11.2.2 Inhalation

Metal fume fever has been reported from inhalation of high copper (metallic) concentrations in occupational settings; the reported copper sulfate NOAEL in mice is 3.3 mg/m³ (Kim et al. 2019; NCBI 2020). The inhalation of copper salt dusts can irritate the respiratory tract (Risk Assessment Information System (RAIS) 1997).

7.11.2.3 Dermal

Dermal exposure to copper has not been associated with toxicity but copper may induce irritation or allergic responses in sensitive individuals (Kim et al. 2019; NCBI 2020).

7.11.2.4 Ocular

Copper salts are reported to cause conjunctivitis, edema of eyelids, and ulceration or turbidity of the cornea (Kim et al. 2019; NCBI 2020).

7.11.2.5 Development and Reproduction

A developmental study using rabbits orally dosed with 0, 6, 9, or 18 mg Cu/kg-day (as copper hydroxide) from days 7 to 28 gestation was reported (ECHA 2021e). Maternal toxicity was observed in rabbits dosed with 9 or 18 mg Cu/kg-day. Fetal effects occurred only at doses that were maternally toxic. The NOAEL was 6 mg Cu/kg-day based on these findings. A two-generation developmental reproductive toxicity test was conducted in rats (ECHA 2021e). The highest dietary treatment was 1,500 ppm (prematuring) and 1,000 ppm during gestation, parturition and weaning (equivalent to 15.2–23.5 mg/kg-day in males and 17.0–35.2 mg/kg-day in females) (ECHA 2021e). No treatment related toxicities that were not secondary to maternal toxicity were observed in any of the doses tested; thus, the NOAEL was 1,000 ppm.

7.11.2.6 Genotoxicity

Copper was negative in an Ames assay up to 1,000 µg/mL; cytotoxicity was observed at 200 µg/mL (ECHA 2021e). Copper was mutagenic at 8.5 mg/kg in a mouse *in vivo* micronuclei and genotoxicity assay (Prá et al. 2008). Copper sulfate has been found to be genotoxic in several *in vitro* and *in vivo* tests (ATSDR 2020c).

7.11.2.7 Carcinogenicity

Copper is listed as IARC category D, not classifiable for human carcinogenicity based on lack of human data and inadequate animal data (Kim et al. 2019; NCBI 2020).

7.11.2.8 Neurotoxicity

Neurological and psychiatric abnormalities are caused mainly by neuronal damage due to copper deposition in the brain. Encephalopathy due to hepatic dysfunction is also occasionally noted. The most frequent symptoms are dysarthria, dystonia, dysdiadochokinesia, bradykinesia, and tremor (Kim et al. 2019; NCBI 2020).

7.11.3 Ecological Data

7.11.3.1 Fate and Transport

While copper salts are often highly soluble, they are strongly adsorbed to suspended particles. Most insoluble and soluble copper compounds are associated with solids and have low mobility in soil, and are not expected to volatilize from water or moist soil surfaces. As an essential nutrient, copper is strongly bioaccumulated by all plants and animals; however, copper compounds are not biomagnified at higher trophic levels.

7.11.3.2 Ecotoxicity

The ambient water quality criteria to protect aquatic life is 5.6 µg/L for freshwater species and 4.0 µg/L for saltwater or marine species, which is expressed as a 24-hour average of total recoverable copper (Kim et al. 2019; NCBI 2020). Shifts in the fish and invertebrate community structures occurred in streams that were experimentally polluted with copper. Sensitive insect species like *Psephenus* (beetle), *Baetis* spp. (mayflies) and *Stenonema interpunctatum* (mayflies) disappeared, and the community was dominated by chironomids (midges) when copper concentrations exceeded 0.052 mg/L (Kim et al. 2019; NCBI 2020).

Copper can apparently be taken up by plants sufficient to cause poisoning in grazing species. Grass hay from pastures fertilized with a manure slurry from pigs that were fed a copper supplement gave rise to poisoning in sheep that ate the hay. The hay in this incident had a copper concentration of 42 ppm. Copper contaminated chicken litter has also been the cause of poisoning in ewes (Kim et al. 2019; NCBI 2020).

The 96-hour LC₅₀ for larval fathead minnows was 250 µg/L total copper and the 28-day LC₅₀ was about 123 µg/L total copper (Kim et al. 2019; NCBI 2020).

Excess copper concentration is used as an algicide, apparently causing an imbalance with metal cofactors resulting in enzyme disruption (Kim et al. 2019; NCBI 2020).

Reported ecotoxicity values include a 14-day EC₅₀ in green algae of 85 µg/L, and a 96-hour LC₅₀ in *Oncorhynchus kisutch* (Coho salmon) of 286 µg/L (Kim et al. 2019; NCBI 2020).

In birds, copper toxicity depends on the copper species and solubility as well as dosing method (gavage/bolus versus feed). A review of the ECOTOX database identified the LD₅₀ for bolus delivery of copper was 693 mg copper sulfate/kg and 1,263 mg copper oxychloride/kg in chickens (Shivanandappa et al. 1983). The LD₅₀ of copper oxide delivered by capsule was greater than 2,250 mg/kg in mallard ducks.

7.11.3.3 Degradation and Treatment

Hydrolysis and precipitation dominate the chemistry of copper compounds at pH values expected in most natural systems in the absence of significant levels of organic complexing ligands. The chemical conditions of most aquatic systems are such that even if relatively large levels of total copper are present, the process of hydrolysis, precipitation, complexation, and adsorption will very often be able to reduce free copper ion concentrations to extremely low values (Kim et al. 2019; NCBI 2020).

7.12 Beta-resorcylic/Salicylic (A Component of LC-12-15)

7.12.1 General Information

β-resorcylic acid (2,4-dihydroxybenzoic acid, 2,4-DHBA) and salicylic acid (2-hydroxybenzoic acid, orthohydroxybenzoic acid, SA) are both hydroxyl-substituted benzoic acids and are naturally produced in some plant species (e.g., sweet birch, avocado, and wintergreen) (Figure

5). Propellant technologies use benzoic acid derivatives as burn rate modifiers. Mixtures of copper or bismuth salts of hydroxy-substituted benzoic acids are effective at flattening the burn rate as a function of pressure, and producing so-called “mesa” burning (“mesa” referring to a flat-topped physical terrain feature). β -resorcylic acid (2,4-dihydroxybenzoic acid, 2,4-DHBA) is used in double base propellant formulations as a burn-rate modifier – most commonly as bismuth (III) β -resorcylate (U.S. Patent No. 5,652,409; 29 Jul 1997). Salicylic acid has many industrial uses in cosmetics and pharmaceuticals (e.g., ointments, creams, gels, transdermal patches). Salicylic acid is the active metabolite of acetylsalicylic acid (i.e., aspirin). Like 2,4-DHBA, salicylic acid, most commonly in the form of copper(II) salicylate, is used as a burn-rate modifier for double base propellants (U.S. Patent 5,652,409, 29 Jul 1997).

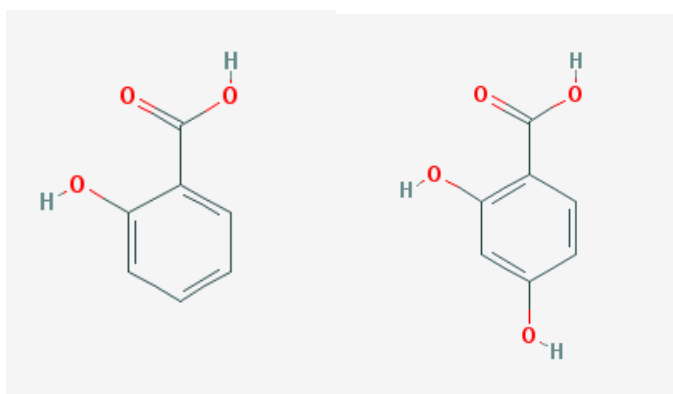


Figure 5. Salicylic Acid (left) and β -Resorcylic Acid (right)

7.12.2 Toxicology Data – β -resorcylic and Salicylic Acids

Much of the available literature for β -resorcylic acid (2,4-DHBA; CAS RN 89-86-1) addresses the compound in the context of aspirin toxicity. When ingested, aspirin is hydrolyzed in the stomach to salicylic acid (salicylate). The oxidative biotransformation products of salicylic acid are the DHBA isomers; 2,3-DHBA (pyrocatechuic acid) and 2,5-DHBA (gentisic acid) are the predominant hydrolytic metabolites of salicylic acid (Bojić et al. 2015). There is a significant body of literature regarding the effects, mode of action and toxicity of aspirin that will not be included for this assessment. Salicylate poisoning (aspirin poisoning or salicylism) occurs from acute or chronic ingestion or dermal exposure of salicylates. It is characterized by a constellation of symptoms including tinnitus (ringing in the ears), nausea, abdominal pain, and a fast breathing rate (Kim et al. 2019; NCBI 2020). Additionally, methyl salicylate (oil of wintergreen) is rapidly and completely hydrolyzed into salicylic acid and toxicology data are available for it (Davison et al. 1961). Due to the chemical relatedness, toxicity endpoints for aspirin and methyl salicylate may inform the toxicity of resorcylate and salicylate. Salicylic acid's production and use as a dyestuff intermediate, in the manufacture of resins, prevulcanization inhibitor, analytical reagent, and in the manufacture of aspirin and salicylates may result in its release to the environment through various waste streams (Kim et al. 2019; NCBI 2020). Its former U.S. use as a fungicide resulted in its direct release to the environment.

In the context of occupational exposure to salicylic acid, this might occur through inhalation and dermal contact with this compound at workplaces where salicylic acid is produced or used. Salicylic acid and the DHBA isomers are endogenously produced by multiple plant species (Hayat et al. 2007; Hayat et al. 2012; Juurlink et al. 2014). Monitoring data indicate that the general population may be exposed to salicylic acid via ingestion of foods containing salicylic acid, which include many fresh or canned vegetables and fruits, herbs and spices, and beverages such as coffee, tea, and red wine.

For convenience, the toxicity data for β -resorcylic acid and salicylic acid are presented together.

7.12.2.1 Oral

Very limited toxicological data for acute, sub-chronic or chronic oral exposure to 2,4-DHBA in animal models or wildlife studies were identified. The LD₅₀ in female Wistar rats was reported to be 3,327 mg/kg (ECHA 2021a). 2,4-DHBA is registered as a GRAS flavoring agent, FEMA #3798 up to 500 ppm in food (Adams et al. 2005). 2,4-DHBA was found to be gastroprotective in a rat ethanol-induced gastric injury model (Trautmann et al. 1991).

Considerably more is known about the oral toxicity from salicylic acid and salicylate derivatives. Salicylic acid has a portal of entry effect – it causes severe gastric irritation. Salicylic acid displays greater irritancy of the gastric mucosa than acetylsalicylic acid and is thus no longer prescribed as an oral therapeutic. Animal model studies of the acute oral toxicity of salicylic acid are available (Kim et al. 2019; NCBI 2020). Groups of five cats were dosed with salicylic acid (Bekemeier 1955). One animal that was given 1.0 g/kg and three others that were given 0.35 and 0.45 g/kg died. All animals given 0.1 to 0.18 g/kg salicylic acid survived treatment. In addition, the LD₅₀ of salicylic acid was reported as 891 mg/kg for rats (Cosmetic Ingredient Review Expert Panel (CIREP) 2003). Oral dosing of 50 mg/rat salicylic acid resulted in gastric lesions and bleeding 1 hour post treatment. In another study, groups of four male albino Wistar rats were orally dosed for 3 days with 500 mg/kg-day salicylic acid in distilled water, pH 7.2. Compared to controls, levels of aniline hydroxylase, glutathione, plasma aspartate aminotransferase (AST), and plasma alanine aminotransferase (ALT) activities were increased and a significant decrease in glucose-6-phosphatase activity (Kim et al. 2019; NCBI 2020). In a separate study, four male albino Wistar rats were administered a single oral bolus dose of 800 mg/kg salicylic acid in distilled water, pH 7.2. Four hours after treatment, a significant increase in liver-to-body weight ratios and plasma ALT levels and a marked decrease in glutathione, compared to controls, were reported (Kim et al. 2019; NCBI 2020).

Extensive literature is available describing the subacute, sub-chronic and chronic oral toxicity of salicylic acid and salicylate derivatives using rodent, canine and rabbit models. In one subacute rodent study, five male Sprague-Dawley rats and five male ICR mice were fed a diet containing salicylic acid for 1 week; the mean daily intake of salicylic acid was 1.48 and 13.7 mmol/kg (200 mg/kg and 1,893 mg/kg) for rats and mice, respectively. Control animals were fed an untreated diet (Kim et al. 2019; NCBI 2020). No significant differences were observed in any of the measured biochemical parameters that contribute to the clotting of blood. The relative weights of the livers in mice, but not rats, were significantly increased compared to the controls.

In a 2-year rodent study, groups of 50 litter-mate Osborne-Mendel rats (25 males/ 25 females per group), were fed a diet containing 0, 0.1, 0.5, 1.0, or 2.0% methyl salicylate (Webb and Hansen 1963). Methyl salicylate is hydrolyzed in the liver to salicylic acid. Body weights were measured weekly and hematological examinations were done on 10 rats per group at 3, 11, 17, and 22 months. Growth retardation was observed in the 2% and 1% treatment groups. All animals in the 2% methyl salicylate group died by week 50. An increase in cancellous bone (spongy bone) was observed in this group and to a lesser extent in the 1% group. Inhibition of bone-remodeling mechanisms, specifically osteoclastic activity, is thought to be the cause of the changes in bone. In an unpublished 2-year feeding study used as part of a safety assessment for the use of methyl salicylate in cosmetics, toxicity was not observed up to 0.21% methyl salicylate (CIREF 2003).

Dogs dosed with capsules containing up to 1,200 mg/kg-day of methyl salicylate resulted in weight loss and death in all dogs on the 500 mg/kg-day level and above (Webb and Hansen 1963). The livers of the dogs on the 1,200 and 800 mg/kg/day levels had moderate to marked degrees of fatty metamorphosis. Dogs given capsules with 350 or 150 mg/kg-day methyl salicylate for 2 years had enlarged livers and increased size of the hepatic cells. The dogs on the higher level lost weight; those on the next higher level showed growth retardation.

A systematic review of the consumption of natural salicylates in foods by a Scottish population found the median intake was approximately 3.8 mg/day (average of median male and female intake) (Wood et al. 2011). The approximate lethal dose of methyl salicylate in children is less than 5 grams (or 4 mL of oil of wintergreen) and the adult LD₅₀ is 500 mg/kg (Kim et al. 2019; NCBI 2020). It has been demonstrated that salicylic acid crosses the placental barrier and it has also been detected in the breast milk of mothers within an hour of consuming aspirin (NCBI 2020).

7.12.2.2 Inhalation

An extensive search of the literature revealed no toxicological data for acute, sub-chronic or chronic inhalational exposure to 2,4-DHBA in animal models or wildlife exposure studies. TOPKAT modeling of inhalation toxicity is not reliable for 2,4-DHBA.

Inhalation toxicity data were available for salicylic acid and methyl salicylate and reviewed in the ECHA registration dossier (ECHA 2021d). The studies were evaluated via weight of evidence, surrogates (read-across), and original study quality and no toxicity to a 1-hour exposure of 0.9 mg/L salicylic acid dust was observed. Using TOPKAT, the predicted LC₅₀ for salicylic acid is 1.47 g/m³-hour. Using the Occupational Safety and Health Administration (OSHA) recommended conversion factor of 0.25 for dusts, the conservative 4-hour LC₅₀ estimate is 368 mg/m³ (OSHA 2016).

In a 1970 study, the inhalation toxicity of methyl salicylate was determined in a group of four female Alderley Park rats (Gage 1970). Animals were exposed to 20 cycles of 7-hour exposure to methyl salicylate vapor at saturation (700 mg/m³; equivalent to 120 ppm). In this study, no toxicity was observed, and the organs appeared normal at necropsy.

7.12.2.3 Dermal

2,4-DHBA skin irritation in New Zealand Rabbits was tested under good laboratory practices (GLP) study conditions; 2,4-DHBA was found not irritating (ECHA 2021b).

The acute dermal LD₅₀ for salicylic acid is > 2,000 mg/kg in rabbits (ECHA 2021f). Groups of three rabbits were dosed dermally with synthetic methyl salicylate 5 days per week for up to 96 days (ECHA 2021d). Doses of 0.5, 1.0, 2.0, or 4.0 mL/kg were applied to intact clipped skin on the back of restrained animals for 6.5 hours each day. The compound was absorbed during the exposure period and the skin surface was not cleaned after the exposure period. All animals in the highest dose group died during the study (days 6, 8, and 28). Necropsy and histological evaluation of tissues from this dose group found kidney, pancreatic, liver and bone marrow effects in one rabbit and only kidney effects in the other two rabbits.

Salicylic acid and methyl salicylate have been evaluated for skin sensitization in the local lymph node assay (LLNA) and guinea pig maximization/Buehler test and in humans (ECHA 2021d, 2021f). Neither were found to be skin sensitizers.

7.12.2.4 Ocular

2,4-DHBA was tested for ocular effects using New Zealand rabbits. The tests were performed consistent with GLP. Based on grade 4 corneal lesions, 2,4-DHBA was scored as GHS category 1 (irreversible effects on the eye) (ECHA 2021b).

Salicylic acid was tested using the Draize method and, like 2,4-DHBA, was found to cause irreversible damage to the eye; GHS category 1 (ECHA 2021f).

7.12.2.5 Development and Reproduction

No experimental data were found for developmental or reproductive effects of 2,4-DHBA. TOPKAT modeling predicts 2,4-DHBA is developmentally toxic.

Salicylic acid is a developmental and reproductive toxicant. Developmental toxicity to methyl salicylate via dermal exposure has also been demonstrated (Overman and White 1983). In this single dose study, pregnant hamsters were dermally treated with 0, 3,500 and 5,250 mg/kg body weight or 1,750 mg/kg orally at 7 days 9 hours gestation. Blood levels of salicylate peaked 2 hours post oral exposure and at 5–6 hours post dermal exposure. Embryos harvested at 9 days gestation were found to have neural tube defects (72% of fetuses in the oral treatment, 6% in the low dose dermal treatment and 53% in the high dose dermal treatment). The researchers stated that these results were consistent with the blood salicylate concentrations (Overman and White 1983).

Salicylic acid was reported to be the causative agent in aspirin teratogenesis in rats (Kimmel et al. 1971). Feeding studies with pregnant Wistar rats (0, 0.06, 0.1, 0.2, or 0.4% salicylic acid from days 8 to 14 of gestation) demonstrated decreased uterine and placental weights and 71.2% neonatal mortality in the 0.4% group as compared to controls (Tanaka et al. 1973). The ratios of resorptions, placental remnants, and implantation sites to the number of implantations were

23.9, 31.4, and 15.9%, respectively. Five dams from each dose group were maintained through weaning of offspring and the offspring were euthanized and necropsied at 56 days old. Litter size was significantly decreased in the 0.4% group. No offspring in the 0.4% group survived more than 24 hours after birth. The remaining groups survived to post-natal day 56. In the offspring, body weight and length were significantly decreased above 0.1% and tail length was significantly decreased above 0.06% salicylic acid. Other adverse effects observed in the offspring included external, internal, and skeletal anomalies in the 0.4% dose group and external and skeletal anomalies in the 0.2% dose group.

A number of *in vitro* teratogenicity studies have been performed on salicylate derivatives, and all have generally produced positive results. Some studies were mechanistic and examined whether the teratogenic effects were due to aspirin or salicylic acid (Yokoyama et al. 1984), or due to salicylate or any of its metabolites (Greenaway et al. 1984).

7.12.2.6 Genotoxicity

No experimental data for 2,4-DBHA were identified. TOPKAT predicts 2,4-DBHA is nonmutagenic.

Multiple *in vitro* genotoxicity/mutagenicity studies of salicylic acid have been conducted. Salicylic acid was not mutagenic in a *Salmonella*/microsome test using *S. typhimurium* strains TA100, TA98, TA1535, and TA1537 with metabolic activation (McCann et al. 1975). Additional Ames assays consistent with salicylic acid being non-mutagenic in bacteria, as well as no mutagenicity in *Saccharomyces cerevisiae* strain rad18 were reported (NIOSH 2018).

Salicylic acid and salicylates were tested using the *B. subtilis* genotoxicity Rec-assay (Kuboyama and Fujii 1992). The Rec-assay may be more sensitive than the Ames assay due to the simultaneous testing of two complementary strains (H17 and M45). In this study, liver microsome fractions from four species were tested. Salicylic acid was weakly positive at and above 2 mg/disc when microsomal fractions from hamster were used.

Euglena gracilis, a less well-known model system for detecting genotoxicity was used to test p- and o-aminobenzoic acids, p-aminosalicylic acid, salicylic acid, sodium salicylate, and acetylsalicylic acid (Foltínová and Grones 1997). *E. gracilis* are aquatic photosynthetic protozoa. In this test system, genotoxicity is measured by the loss of chlorophyll that results in bleached cells. A decrease in genotoxicity (antimutagen) may be measured in this test system by using the test chemical to rescue the cells from a known mutagen (e.g., N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and N-methyl-N-nitroso urea (MNU)). Salicylic acid did not induce bleaching up to 1200 μ M (the highest dose tested). At concentrations from 50–500 μ M and 200–1,200 μ M, salicylic acid reduced the genotoxicity of MNNG and MNU, respectively. The mechanism for this antimutagenic phenomenon is not characterized.

Salicylic acid was negative in an *in vitro* chromosome aberration assay using CHO cells (Chinese hamster ovary cells) both with and without metabolic activation up to 25 mg/mL (Stich et al. 1981). The addition of the divalent cations Cu^{2+} and Mn^{2+} did not alter the percentage of metaphases with chromosomal aberrations induced by 12 mg/mL of salicylic acid.

SCE and chromosome aberrations experiments were performed using bone marrow cells of male Swiss albino mice (Giri et al. 1996). Acetyl salicylic acid and sodium salicylate showed weak genotoxicity at the highest dose tested by both IP (100 mg/kg) and oral (350 mg/kg) routes while salicylic acid was not genotoxic under the same conditions.

7.12.2.7 Carcinogenicity

No data for carcinogenic effects from exposure to 2,4-DHBA were identified in the literature.

Methyl salicylate was tested as part of a large pulmonary tumor study using a mouse model (Stoner et al. 1973). The mouse lung tumor model compares the number of lung tumors generated in mice treated with a known carcinogen (urethane) to mice treated with the test chemical, vehicle treated, and untreated mice. A/He mice were injected three times per week for 8 weeks for a total of 24 doses and then observed for an additional 16 weeks before euthanasia and necropsy. All mice treated with the positive control developed multiple lung tumors. Mice treated with methyl salicylate did not show an increase in tumors above the spontaneous and vehicle-treated groups.

Salicylic acid and acetylsalicylate (aspirin) have been identified as potential chemopreventive agents for colorectal cancer (Williams et al. 1997). Although the mechanism(s) have not been elucidated, evidence thus far suggests salicylates downregulate proteins important for cell cycle regulation (Dachineni et al. 2016).

7.12.2.8 Neurotoxicity

No toxicological data for neurological effects from exposure to 2,4-DHBA in animal models or wildlife studies were identified in the literature.

Salicylates are known to be ototoxic (having a toxic effect on the ear or its nerve supply) and at high doses induce tinnitus and sensory hearing loss (Sheppard et al. 2014). Salicylate is used as a positive control in animal models for tinnitus; however, the effect in humans is much more variable. Transient tinnitus and hearing loss has been reported in individuals taking high doses of aspirin over a period of 2–4 days (Sheppard et al. 2014). In rats, it is postulated that sodium salicylate impacts GABA-A (γ-aminobutyric acid A) – NMDA (N-methyl-D-aspartate) signaling in the cochlear spiral ganglion neurons (Liu et al. 2019). The mechanism for ototoxicity in humans is not fully understood.

7.12.3 Ecological Data

7.12.3.1 Fate and Transport

The 2,4-DHBA and SA have experimental database entries in EPI Suite 4.11; 2,4-DHBA is more water soluble than SA (5780 mg/L versus 2240 mg/L). EPI Suite was used to model 2,4-DHBA fate and transport. In water, 2,4-DHBA is soluble and binds moderately to carbon/particulates so will have some potential to transport in surface water. The log K_{oc} is 1.39 indicating 2,4-DHBA will not be tightly bound to soil and could enter groundwater. With a vapor pressure of 6.69×10^{-8} the volatilization of 2,4-DHBA from aquatic media will not occur. 2,4-DHBA will not

exist as a vapor in air and will be bound to particulates. For 2,4-DHBA that is released to air, hydroxylation is rapid and the half-life of 2,4-DHBA is 38 minutes; the fraction adsorbed to particulates may be resistant to atmospheric oxidation.

If released to the air, SA will exist in both the vapor and particulate phases in the atmosphere. Vapor phase SA will be degraded by hydroxylation; the half-life for this reaction in air is estimated to be 30 hours. Particulate-phase SA will be removed from the atmosphere by wet or dry deposition. Salicylic acid contains chromophores that absorb at wavelengths greater than 290 nm and therefore may be susceptible to direct photolysis by sunlight (NCBI 2020).

If released to the soil, salicylic acid is expected to have moderate mobility in soil based upon an estimated log K_{OC} of 2.61 and water solubility of 2.2 g/L. The pKa of salicylic acid is 2.98, which indicates that this compound will exist primarily in the anionic form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts. Salicylic acid is not expected to volatilize from dry soil surfaces based upon its vapor pressure of 8.2×10^{-5} mm Hg at 25°C, and it has been observed to biodegrade quickly under differing sets of agricultural practices in Pahokee muck soil, which suggests that biodegradation in soil is an important fate process (NCBI 2020). Volatilization from either wet or dry soil is not expected to be an important fate process for SA.

If released into water, salicylic acid is expected to adsorb to suspended solids and sediment based upon the estimated log K_{OC} of 2.61, using a log K_{OW} of 2.26 and a regression-derived equation. In addition, a pKa of 2.98 indicates that salicylic acid will exist almost entirely in the anion form at pH values of 5 to 9 and thus volatilization from water surfaces is unlikely to be an important fate process (NCBI 2020).

7.12.3.2 Ecotoxicity

Limited data are available on the impact of 2,4-DHBA on wild animals and plants. 2,4-dihydroxybenzoic acid had an EC_{50} to *D. magna* of 188 mg/L for a 24-hr exposure and 120 mg/L for a 48-hr exposure (Kamaya et al. 2005). In a 72-hour lettuce seed germination test, 2,4-DHBA had an EC_{50} for germination inhibition of 1.23 mM (Reynolds 1978).

2,4-DHBA has been evaluated as a prebiotic dietary supplement in chickens to reduce *Campylobacter* colonization (Wagle et al. 2017). In this study, up to 1% 2,4-DHBA was provided in the diet for 14 days without clinical signs of toxicity. These data suggest negligible toxicity from 2,4-DHBA at ecologically relevant concentrations.

SA has been more extensively studied. The SA (99.5% pure) *D. magna* 24-hour EC_{50} is 1,060 mg/L (static conditions/21°C/pH 7.45) and the 48-hour *D. magna* EC_{50} is 870 mg/L (Kamaya et al. 2005). In green algae, the 48-hour EC_{50} for population effects was 12.3 mg/L in *Raphidocelis subcapitata* (ECOTOX 2009). The SA LC_{50} in golden orfe fish was 90 mg/L and in nematodes (*Meloidogyne arenaria*) the 24-hour LC_{50} was 132–207 mg/L.

Aspirin and SA have been used in veterinary medicine as anti-inflammatory drugs. Limited safety studies were identified in the literature; however, one report found that short term treatment with 10 mg aspirin/kg was toxic to the hemotologic and digestive systems in domestic

chickens (Mohan et al. 2012).

7.12.3.3 Degradation and treatment

In aqueous biodegradation screening tests, salicylic acid reached 88.1% of its theoretical biological oxygen demand after 14 days, suggesting that biodegradation in water is an important fate process. 2,4-DHBA was demonstrated to be very biodegradable with 70% elimination within 10 days (ECHA 2021b).

The potential for bioconcentration of SA in aquatic organisms is low based on a BCF of 3 and log K_{OW} of 2.26 (NCBI 2020). 2,4-DHBA hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions. Additionally, half-lives of 30 to 142 days have been calculated for the photochemical reaction of salicylic acid and the salicylate with hydroxyl radicals in full intensity sunlit natural waters (NCBI 2020). Limited evidence suggests that salicylic acid, via photochemical processes, is involved in polymerization of fulvic acids in natural waters (NCBI 2020).

8 DISCUSSION

8.1 Compound Assessments

Using the categorization criteria and color coding schemes from the Tables in Appendix B, the compounds were scored and presented as a chicklet table where red is the least desirable and green is the most desirable rank; see Table 2. Note, GHS categorization is provided for each endpoint and compound when it was available. In Table 2, column titles denoted with a “¹” (superscript “1”) have a 5-color scale (magenta (highest hazard) to green (lowest hazard)). columns denoted with a “²” (superscript “2”) have a 4-color scale (red (highest hazard), orange, yellow, green (lowest hazard)). GHS categories for acute toxicity (oral, inhalation and dermal) do not have a category for compounds considered non-toxic (see Appendix B, Table B-2). GHS scores for skin corrosion/irritation, eye effect, cancer, and acute/chronic aquatic toxicity have a “not categorized” category – colored green – that doesn’t have a number associated with it. In other words, only compounds with toxicity will have a GHS numbered category (e.g., 1, 2A, 2B, I, II, III). For toxicity categories not covered by the GHS classification scheme, the APHC hazard scheme is used; column titles are denoted with a “³” (superscript “3”). The APHC hazard scheme uses a 3-color format (red, yellow, green) to indicate highest hazard (red) to moderate hazard (yellow) to low hazard (green). Specific examples of these caveats are the entries for nitrocellulose and candelilla wax in Table 2.

8.1.1 Nitrocellulose

As a high molecular weight polymer, nitrocellulose is insoluble and therefore not bioavailable. The primary toxicological concern stems from potential exposure to the nitrate groups on the molecule, possibly resulting in CNS depressant effects. Occupational health concerns are relatively minor, and can be addressed by proper use of appropriate personal protective equipment to limit exposure.

8.1.2 Nitroglycerine

Nitroglycerine is a common medication for treatment of angina and coronary artery disease, with moderate toxic effects. Exposures can result in vasodilation, which is the basis for its medicinal effect. Exposed workers may exhibit headaches and methemoglobinemia; bradycardia is observed in some cases. Tolerance develops, and withdrawal from long-term exposure can result in cardiovascular problems, including death. Overall, NG presents only a moderate hazard to workers and the environment.

8.1.3 Triacetin

Triacetin is not expected to be toxic by any exposure route under expected exposure conditions.

8.1.4 DNPA

DnPA is not expected to be toxic via all exposure routes and pose little environmental hazard.

8.1.5 2-NDPA

Acute toxicity of 2-NDPA via oral, inhalation, or dermal exposure does not appear to be a hazard. Occupational exposure hazards to skin and eye appear to be moderate. Due to the potential risks to aquatic species, a luminescent bacteria screen is recommended, and untreated discharge to water is not recommended. Waste streams can probably be significantly reduced by physical and biological treatment.

Table 2. ALR 17-02 Formulation ESOH Assessment and Regulatory Status

Chemical Substance	Human Health and Ecological Assessment*													
	Oral ¹	Inhalation ¹	Dermal ¹	Ocular ²	Carcinogenicity ²	Aquatic ²	Invertebrates ²	Plants ³	Mammals ³	Birds ³	Persistence ³	Transport ³	Bioaccumulation ³	Regulations
Nitrocellulose		P	3	2B						P				No
Nitroglycerin	4	4	2 [†]	2B		II	III							Skin: NIOSH REL, OSHA REL, IDLH, EPA (water) water, CERCLA, RCRA
Triacetin	4	4	P	2B	P			P	P	P				No
DnPA	P	P	P	P	P	II	II	P	P	P				No
2-NDPA	4	**	2	2		II	II	P	P	P				No
Candelilla wax														No
Carbon black		**			2B									NIOSH 8-hr TWA, OSHA PEL, IDLH
LC-12-15-Lead	4	DE			2B	I	II		NT					ACGIH TLV/TWA, OSHA BLL, CDC BLL, EPA (air, soil, water)
LC-12-15-Copper	4	**				I	I							ACGIH/OSHA TWA, EPA (water)
LC-12-15- β-RA	5	P	3	1					DT					No
LC-12-15-SA	4	P	3	1		III			DT					OSHA TWA

Legend:

P=predicted based on *in silico* data, read-across, expert opinion, percent formulation and usage; †=dermal toxicity and sensitizer

DE=delayed effects; DT=developmental toxicant; NT=neurotoxicant

Notes:

*Annotated with key hazards and critical endpoints. See Appendix B for further information on the hazard codes and color schemes.

** = irritant

¹ GHS Categories and color warning charts for acute oral, acute inhalation, and skin corrosion/irritation included when available:  magenta (highest) >  red >  orange >  yellow >  green (lowest) toxicity.

² GHS Categories and color warning charts for eye irritation, cancer and aquatic toxicity included when available:

 red (highest) >  orange >  yellow >  green (lowest) toxicity.

³ APHC hazard categorization criteria  red (highest) >  yellow >  green (lowest) concern.

8.1.6 Candelilla Wax

The consistent absence of adverse effects in toxicity tests indicates that there are no toxicological hazards from candelilla wax in its functional uses (i.e., as a glazing agent, component of chewing gum base, surface finishing agent, or flavor carrier).

8.1.7 Carbon Black

Carbon black is essentially non-toxic, but particle inhalation should be avoided. A respirator appropriate to the ambient airborne carbon black concentration is recommended in an occupational environment (NIOSH 2019b). Ecotoxicity is not a concern for this chemical.

8.1.8 Lead

Lead toxicity in human populations and other terrestrial and aquatic animals is well reported with key routes of exposure to human populations being via the oral and inhalational pathways. Adverse neurological, hematological, cardiovascular and developmental effects are observed in humans and animal models. Lead has no known biological or physiological functions and is not a dietary required nutrient and widespread dispersion of lead in the environment – primarily due to anthropogenic activity.

8.1.9 Copper

Copper is an essential nutrient that has low toxicity towards mammals and many other species. The exception is aquatic invertebrates and algae; releases to aquatic media should be avoided. The toxicity of copper is usually seen when *in vivo* concentrations exceed homeostatic regulation.

Excess levels of copper exert their effect by disrupting the structural and functional integrity on biologically important molecular building blocks including DNA, cellular membranes, and proteins and can do so either by directly-mediated effects or via the generation of reactive oxygen species and free radicals.

Oral toxicity generally increases with solubility and adverse health effects include gastric hemorrhage, tachycardia, hypotension, hemolytic crisis, convulsions, and paralysis followed by death.

By inhalation, metal fume fever has been reported following respiratory exposure to high concentrations in the air from occupational settings.

Dermal exposure is not known to provoke any adverse health outcomes – though allergic contact sensitivity cannot be ruled out. Copper salts are reported to provoke conjunctivitis, edema of the eyelids and ulceration or turbidity of the cornea.

8.1.10 Beta-resorcyate/Salicylate (A Component of LC-12-15)

Although beta-resorcyate/salicylate is expected to be combusted during deployment of this

formulation, the potential for toxicity from occupational and potentially environmental exposure to these compounds was considered. Direct skin exposure to resorcyate/salicylate may cause irritation and ocular exposure may cause severe irritation or permanent eye damage. Resorcyate/salicylate dust may be a respiratory irritant. Skin and eye exposure should be avoided. Appropriate personal protective equipment (respiratory, skin, and eye) should be used. Individuals with aspirin sensitivity should avoid contact with salicylate.

8.2 Regulations and Standards

A review of ACIGH, OSHA, NIOSH, PubChem safety and hazard tables was conducted. The information provided in this section represents the findings at the time of the review and should always be confirmed with the most recent documentation provided by these agencies.

8.2.1 Nitrocellulose

No regulations or standards pertaining to nitrocellulose were found.

8.2.2 Nitroglycerine

NIOSH REL: short-term 15-minute exposure limit is 0.1 mg/m³ (skin); the time-weighted average (TWA) is 0.05 ppm, skin; OSHA permissible exposure limit (PEL) 2 mg/m³ (0.2 ppm), skin. The Immediately Dangerous to Life and Health (IDLH) concentration is 75 mg/m³ (NIOSH 2019a).

The EPA has established a Federal Drinking Water Guideline for NG at a concentration of 5 µg/L (Leikin et al. 2007).

Release of more than 10 pounds (4.54 kg) of NG is reportable under the Comprehensive Environmental Responsibility and Liability Act (CERCLA; also known as Superfund). When NG becomes a waste, it is subject to management under the Resource Conservation and Recovery Act (RCRA) (NCBI 2021b).

8.2.3 Triacetin

GRAS for human consumption without limitation other than for current good manufacturing practice (CFR 2020a) (Fiume 2003).

8.2.4 DNPA

No regulations or standards pertaining to DnPA were found.

8.2.5 2-NDPA

No regulations or standards pertaining to 2-NDPA were found.

8.2.6 Candelilla Wax

No regulations or standards pertaining to candelilla wax were found.

8.2.7 Carbon Black

The IDLH is 1,750 mg/m³; NIOSH 8-hr TWA 3.5 mg/m³ for inhaled carbon particles. The OSHA PEL is 3.5 mg/m³ (NIOSH 2019a).

8.2.8 Lead

The ACGIH, CDC, EPA, FDA, NIOSH, and OSHA have published standards for lead (ATSDR 2021). The ACGIH threshold limit value (TLV[®])/TWA is 50 µg/m³ (equivalent to a BLL of 30 µg/dL) and the OSHA workplace action level (averaged 8-hour) is 30 µg/m³ (the OSHA actionable BLL is 40 µg/dL). These OSHA levels trigger medical surveillance. For children, the CDC reference BLL is 5 µg/dL. The EPA air standard (3-month average) is 0.15 µg/m³ and the soil screening level is 400 ppm for play areas and 1,200 ppm for non-play areas. The EPA drinking water action level is 15 µg/L, (the FDA bottled water standard is 5 parts per billion).

Lead compounds are designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act (40 CFR 116.4; (EPA 2005)) including lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead sulfate, lead sulfide, and tetraethyl lead.

8.2.9 Copper

The EPA has established a 1-day health advisory for copper in drinking water at 1.3 mg/L (EPA 2021). The permissible concentration of total recoverable copper in water to protect freshwater aquatic life is 5.6 µg/L as a 24-hour average (NCBI 2020). The ACGIH has established an 8-hour TWA of 0.2 mg/m³ for copper fumes and 1 mg/m³ for copper dusts. OSHA has established an 8-hour TWA of 0.1 mg/m³ for copper fumes and 1 mg/m³ for dusts (NIOSH 2019a).

8.2.10 Beta-resorcyate/Salicylate (A Component of LC-12-15)

No regulatory values were identified for 2,4-DHBA. 2,4-DHBA is registered as GRAS flavoring agent, FEMA #3798 up to 500 ppm in food.

An OEL has not been established for salicylic acid. The OSHA 8-hour TWA for acetylsalicylic acid (aspirin) is 5 mg/m³ (NIOSH 2018). This limit is expected to protect workers from experiencing the adverse blood effects and gastric and respiratory irritation due to acetylsalicylic acid exposure.

8.3 Formulation Summary

Based upon known or estimated properties of substances or structurally-similar surrogates, conditions, and quantities of projected use, the 2.75" Rocket Motor formulation evaluated in this report is expected to pose some significant human health and environmental concerns. The priority concern is potential inhalational lead exposure during the firing of these rocket motors. There is anecdotal evidence that aircrew involved in firing of the current version of these rockets can smell the exhaust produced. Lead exposures may have sufficient impact to limit aircrew exposure.

9. RECOMMENDATIONS

The formulation addressed in this assessment is a potential hazard to the environment and human health. Specifically, the presence of lead and copper may be hazardous to workers and Soldiers. It is recommended that air quality parameters be addressed to demonstrate that lead and copper are not inhalation hazards. Monitoring of airborne lead levels in aircrew cockpits is recommended. Toxicity data gaps exist for 2-NDPA, DNPA and 2,4-DHBA. However, since these compounds are used in very limited quantities, the hazards from exposures are suspected to be minimal. If there is a potential for environmental release these compounds, then aquatic toxicity testing is recommended.

10. POINT OF CONTACT

The Point of Contact for this report is Dr. Valerie H. Adams, telephone 410-436-3980, DSN: 584-3980.

U.S. Army Public Health Center (APHC)
Toxicology Directorate
Health Effects Division
ATTN: MCHB-PH-HEF
Aberdeen Proving Ground, MD 21010-5403
Phone: (410) 436-3980

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Mark A. Williams, Ph.D., FAAAAI
Biologist, HEF

Date

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William S. Eck, Ph.D.
Biologist, HEF

Date

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Valerie Adams, Ph.D. DABT
Biologist, HEF

Date

Approved by:

QUINN.MICHAEL
L.J.1282372092

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Michael J. Quinn, Jr., Ph.D.
Division Chief, HEF

Date

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Mark S. Johnson, Ph.D., D.A.B.T.
Director, Toxicology Directorate

Date

APPENDIX A

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APPENDIX B

ENVIRONMENTAL SAFETY AND OCCUPATIONAL HEALTH SEVERITY CATEGORIZATION

B-1. APHC CATEGORIZATION CRITERIA

Table B-1. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity (modified from Howe et al. 2006)

	Low	Moderate	High	Unknown
PERSISTENCE	Readily biodegrades (<28 days)	Degradation ½ life: water <40 days , soil <120 days	Degradation ½ life: water >40 days, soil > 120 days	Data are unavailable, insufficient, or unreliable
TRANSPORT	Water sol. < 10 mg/L log K _{OC} > 2.0	Water sol. 10–1,000 mg/L log K _{OC} 1.0-2.0	Water sol. > 1,000 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 (IARC group 3 & 4); Subchronic LOAEL > 200 mg/kg-d	Mixed evidence for carcinogenicity/ mutagenicity (IARC group 2B); Subchronic LOAEL 5-200 mg/kg-d	Positive corroborative evidence for carcinogenicity /mutagenicity (IARC group 1 & 2A); LOAEL < 5 mg/kg-d	
ECOTOXICITY	Acute LC ₅₀ /LD ₅₀ >1 mg/L or 1,500 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 1,500 - 150 mg/kg; Subchronic EC ₅₀ 100 - 10 µg/L or LOAEL 10 -100 mg/kg-d	Acute LC ₅₀ /LD ₅₀ <100 µg/L or <150 mg/kg; Subchronic LOAEL <10 mg/kg-d	

Legend:

mg/L = milligrams per liter

LOAEL =lowest-observed adverse effect level

LC₅₀ = concentration expected to result in 50% lethality to a population of test animals

IARC = International Agency for Research on Cancer

mg/kg-d =milligrams per kilogram per day

µg/L =micrograms per liter

B-2. GLOBALLY HARMONIZED SYSTEM

GHS is the acronym for the Globally Harmonized System of Classification and Labeling of Chemicals. The GHS attempts to establish international consensus for defining health, physical, and environmental hazards of chemicals; creates a classification process for comparison with defined hazard criteria; and communicates hazard information and protective measures on labels and Safety Data Sheets (SDS), (formerly known as Material Safety Data Sheets). 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 United Nations General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While there are several aspects of the GHS, the most important area for our purpose 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 in Tables B-2 through B-6. More information can be found in the original source (UNECE 2015).

Table B-2. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2,000	Criteria: - Anticipated LD ₅₀ between 2,000 and 5,000 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 ≤1,000	>1,000 ≤2,000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2,500	>2,500 ≤5,000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts and Mists (4-hour mg/L or g/m ³)	≤0.05	>0.05 ≤0.5	>0.5 ≤1.0	>1.0 ≤5	

Legend:

mg/kg = milligrams per kilograms

ppm = parts per million

mg/L = milligrams per liter

LD₅₀ = dose resulting in 50% mortality

Table B-3. GHS Skin Corrosion/Irritation

Category 1A	Category 1B	Category 1C	Category 2	Category 3	Not Categorized
Corrosion < 3 minutes Observation < 1 hour	Corrosion < 1 hour Observation < 14 days	Corrosion < 4 hours Observation < 14 days	Irritation Reversible adverse effects in dermal tissue Draize score: ≥ 2.3, <4.0, or persistent inflammation	Mild Irritation Reversible adverse effects in dermal tissue Draize score: ≥ 1.5, <2.3	Corrosion and irritation not observed
Destruction of dermal tissue; visible necrosis in at least one animal.					

Table B-4. GHS Eye Effects

Category 1	Category 2A	Category 2B	Not categorized
Irreversible damage 21 days after exposure	Irritant Reversible in 21 days	Mild irritant Reversible in 7 days	Non-irritating

Table B-5. GHS Acute and Chronic Aquatic Toxicity

Table 2.0: Chronic Acute and Chronic Aquatic Toxicity				
Acute Aquatic Toxicity				
Category I	Category II	Category III		Not Categorized
Acute toxicity ≤ 1.00 mg/L	Acute toxicity > 1.00 but ≤10.0 mg/L	Acute toxicity > 10.0 but < 100 mg/L		Acute toxicity > 100 mg/L
Chronic Aquatic Toxicity when biodegradation ½ life is > 7 days				
Category I	Category II	Category III	Category IV	Not Categorized
Acute Cat I and log K _{ow} ≥ 4, unless BCF < 500; Or chronic toxicity ≤ 0.01 mg/L	Acute Cat II and log K _{ow} ≥ 4, unless BCF < 500; Or chronic toxicity 0.01-0.1 mg/L	Acute Cat III and log K _{ow} ≥ 4, unless BCF < 500; Or chronic toxicity 0.1-1.0 mg/L	Acute toxicity > 100.0 mg/L, biodegradation ½ life >7 days, and log K _{ow} ≥ 4, unless BCF < 500; Or chronic toxicity > 1.0 mg/L	Acute toxicity >100 mg/L, Log K _{ow} < 4, BCF< 500 and chronic toxicity > 1.0 mg/L

Legend:

mg/L = milligrams per liter

BCF = Bioconcentration factor

Table B-6. GHS Carcinogenicity

Category 1A	Category 1B	Category 2	Not categorized
Known to have carcinogenetic potential for humans (human evidence)	Presumed human carcinogens (animal evidence)	Suspected human carcinogen (human or animal evidence but not sufficiently convincing to place in category 1)	No evidence for carcinogenicity.

APPENDIX C
DATA TABLES

Table C-1. Physicochemical Properties

	Molar Mass (g/mol) ^a	Melting Point (°C)	Boiling Point (°C)	Aqueous solubility (mg/L) @ 25°C	Log K_{ow}	Log K_{oc}	Henry's Law Constant (atm- m³/mol) @ 25°C	Vapor Pressure mmHg @ 25°C
Nitrocellulose	Varies with polymer length	n/a	34 ^b	Insoluble ^b	n/a	n/a	n/a	n/a
Nitroglycerin	227.09	13.5 ^b	218 ^b (explodes)	204 ^b	1.62 ^b	1.41 ^c	1.77E-06 ^d	3.0E-04 ^b
Triacetin	218.21	-78 ^b	259 ^b	5.8E+04 ^b	0.25 ^b	1.6 ^b	1.23E-08 ^b	2.48E-03 ^b
DnPA	230.3	-15.7 ^b	261.71 ^c	230 ^d	3.35 ^e	2.65 ^c	3.03E-06 ^c	7.21E-03 ^c
2-NDPA	214.22	75 ^b	346 ^d	0.0011 ^b	3.66 ^d	3.43 ^d	9.07E-08 ^c	1.0E-05 ^d
Candelilla wax	Varies with degree of polymerization	68.5-72.5 ^e	nd	Insoluble ^e	n/a	n/a	n/a	n/a
Carbon black	12.01	Sublimes ^b	4200 ^b	Insoluble ^b	n/a	n/a	n/a	n/a
Lead	207.21	327.4 ^b	1740 ^b	Insoluble	n/a	n/a	n/a	n/a
Copper	63.54	Variable	Variable	Variable	Negligible	Negligible	Negligible	Negligible
Beta-resorcylic acid	154.12	226 ^f	Decomposes @ 290 ^f	5780 ^f	1.63 ^f	1.39 ^c	1.48E-12 ^c	6.69E-08 ^f
Salicylic acid	138.12	158.6 ^b	211 ^b	2240 ^b	2.26 ^b	2.61 ^c	7.34E-09 ^c	8.2E-05 ^d

Legend: g/mol = grams per mole; °C = degrees Celsius; mg/L = milligrams per liter; Log K_{ow} = Log Octanol-water partition coefficient; Log K_{oc} = Log Organic carbon partition coefficient; atm-m³/mol = atmosphere cubic meters per mole; mmHg = millimeters of mercury; n/a = not applicable

Notes: ^a Calculated from molecular formula and standard atomic weights; ^b NCBI 2020; ^c EPA 2013; ^d Williams et al. 2017; ^e IPCS 2009; ^f ECHA 2021b

Table C-2. Toxicity Data

Compound	Acute Oral LD ₅₀ (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation (g/m ³ -h)	Dermal	Ocular	Mutagenicity	Carcinogenicity
Nitrocellulose	>5000 ^a	4866 ^b	Not applicable	Irritant ^a	Irritant ^a	Negative ^a	Negative ^a
Nitroglycerin	822 ^a (rat) 1188 ^a (mouse)	34 ^a (rat, NOAEL)	No data	Mild irritant	Indeterminant ^c	Positive ^a	Negative for tumor promotion ^a
Triacetin	3000 ^a (rat) 1100 ^a (mouse)	No data	0.533 ^c	Possible mild irritant ^a	Possible mild irritant ^a	Negative ^a	Negative ^c
DnPA	6600 ^c	662 ^c	5.9 ^c	Negative ^c	Negative ^c	Negative ^c	Negative ^c
2-NDPA	6150 ^d 980 ^c (rat)	63.1 ^c	1.3 ^c	Possible sensitizer ^c	Mild irritant ^a	Negative ^e	Unlikely ^c
Candelilla wax	>5000 ^f	No data	Not applicable	No data	No data	Negative ^f	No data
Carbon black	>15,400 ^a (rats)	20 ^a (mouse; 4 weeks)	nd	LD ₅₀ >3000 mg/kg (rabbits) ^a	Mild irritant ^h	Positive ^a	IARC 2B ^g
Lead (in LC-12-15)	1400 ^a (PbO; dogs) 1947 ^a (PbCl ₂ ; rats) 115 ^a (LD _{low} , human)	0.10 ⁱ (monkey)	0.271 (human, lowest lethal conc.) ^a	Dermal absorption minimal ^a	Damage and loss of retinal rod cells ^a	Positive (at doses considered toxic) ^a	Inorganic lead compounds are likely carcinogenic by oral or inhalational exposures ^a
Copper (Cu ^{+1/+2}) (in LC-12-15)	Copper acetate ^a 501 (rat), 196 (mouse), 250 (rabbit)	600 ppm ^j (rat, feed)	NOAEL 3.3 mg/m ³ (mouse) ^k	Irritant ^a	Irritant ^a	Genotoxic (CuSO ₄) ⁿ	Adverse health effects from copper deficiency, daily intake 0.9-2.2 mg/day ^a
Beta-resorcylic Acid) (in LC-12-15)	3327 ^l (rat)	353 ^c	1.57 ^c	>2000 ^l	Strong irritant ^c	Negative ^c	Negative ^c
Salicylic acid (in LC-12-15)	480 ^a (mouse) 891 ^a (rat) 400 ^a (cat) 1300 ^a (rabbit)	150 ^m (NOEL; rat)	0.90 (NOEL; rat) ^a 1.47 ^c	> 2.0 gm/kg LD ₅₀ (rat) ^m	Strong irritant ^a	Reproductive toxicant ^a	Negative ^m

Legend: mg/kg = milligrams per kilogram; mg/kg-d = milligrams per kilogram per day; g/m³ = grams per cubic meter;

NOAEL = No Observed Adverse Effect Level; LD₅₀ = dose resulting in 50% mortality; LD_{low} = lowest lethal dose;

NOEL = No Observed Effect Level; mg/day = milligrams per day

Notes: ^a NCBI 2020; ^b In smaller species, death due to intestinal blockage (Ellis et al. 1980); ^c TOPKAT model prediction; ^d USAMRDC 1979;

^e CCRIS 2018; ^f IPCS 2009; ^g Baan 2007; ^h Scheepers and Bos 1992; ⁱ Rice and Gilbert 1985; ^j Sugawara et al. 1995; ^k ATSDR 2020c);

^l ECHA 2021b; ^m ECHA 2021f

GLOSSARY

2,4-DHBA	2,4-dihydroxybenzoic acid
2-NDPA	2-nitrodiphenyl amine
AERTA	Army Environmental Requirement and Technology Assessment
ACGIH	American Conference of Governmental Industrial Hygienists
ALT	Alanine Aminotransferase
ALTBIB	Animal Testing Alternatives
APHC	U.S. Army Public Health Center
AR	Army Regulations
AST	Aspartate Aminotransferase
ATSDR	U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry
BCF	Bioconcentration Factor
BEHA	Bis(2-Ethylhexyl) Adipate
BLL	Blood Lead Concentrations
Bp	Boiling Point
°C	Degrees Celsius
CAS RN	Chemical Abstracts Service Registry Number
CERCLA	Comprehensive Environmental Responsibility and Liability Act
CCRIS	Carcinogenesis Research Information System
CNS	Central Nervous System
cm	Centimeter
CPDB	Carcinogenic Potency Database
CFR	Code of Federal Regulations
CTD	Comparative Toxicogenomics Database

Cu	Copper
DART	Developmental and Reproductive Toxicology Database
DBA	Dibutyl Adipate
DEA	Diethyl Adipate
dL	Deciliters
DNA	Deoxyribonucleic Acid
DnOA	Di-N-Octyl Adipate
DNPA	Di-N-Propyl Adipate
DOD	Department of Defense
DoDI	Department of Defense Instruction
DTIC	Defense Technical Information Center
ECOSAR	Ecological Structure Activity Relationship
EC ₅₀	Median (50%) Effect Concentration
EPA	U.S. Environmental Protection Agency
EPISuites	Estimation Programs Interface (EPI) Suite™
ESOH	Environmental Safety and Occupational Health
FEMA	Federal Emergency Management Agency
FDA	U.S. Food and Drug Administration
ft ³	Feet cubed
GHS	Global Harmonization System
GLE	Gestational Lead Exposure
GLP	Good Laboratory Practices
GRAS	Generally Recognized as Safe
K _H	Henry's law constant

HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IDLH	Immediately Dangerous to Life and Health
IP	Intraperitoneal
IRIS	Integrated Risk Information System
kg	Kilogram
L	Liter
LC-12-15	Lead, Copper, beta-resorcylate salicylate complexes
LC ₅₀	Median (50%) Lethal (Oral) Concentration
LD ₅₀	Median (50%) Lethal (Oral) Dose
LH	Luteinizing Hormone
LLNA	Local Lymph Node Assay
log K _{OC}	Log Organic carbon partition coefficient
log K _{OW}	Log Octanol-water partition coefficient
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest-Observed Adverse Effect Level
m ³	Cubic Meter
µg	Micrograms
µL	Microliter
µM	Micromolar
µm	Micrometer
µmol	Micromole
mg	Milligram
mmHg	Millimeters (mm) Of Mercury (Hg)

mL	Milliliter
mM	Millimolar
mmol	Millimole
MW	Molecular Weight
n/a	Not Applicable
NC	Nitrocellulose
nd	No Data
NG	Nitroglycerin
NIH	National Institutes of Health
NIOSH	U.S. National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	Nanometers
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No-Observed Adverse Effect Level
NOEL	No-Observed Effect Level
NOES	National Occupational Exposure Survey
NPL	National Priorities List
NTP	U.S. National Toxicology Program
OSHA	Occupational Safety and Health Administration
Pb	Elemental lead
PEL	Permissible Exposure Limit
ppm	Parts per million (10^{-6})
PPRTV	Provisional Peer Reviewed Toxicity Value
QSAR	Quantitative Structure-Activity Relationship

RCRA	Resource Conservation and Recovery Act
RDT&E	Research, Development, Technology, and Evaluation
SA	Salicylic acid
SAFR	Safer Alternatives for Readiness
SCE	Sister Chromatid Exchange
SMILES	Simplified Molecular-Input Line-Entry System
SDS	Safety Data Sheet
TOPKAT	Toxicity Prediction Komputer Assisted Technology
TWA	Time-Weighted Average
vp	Vapor pressure