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Toxicology Assessment for SERDP WP22-3235: Benign Phosphorous Polymer-Based Fire Suppression Additives; Functional Additives and Foam Formation to Enhance PFAS-Free Fire Suppressants for Military Use

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14. ABSTRACT
Multiple facilities are investigating the feasibility of utilizing fluorine-free AFFF as replacements to fluorine-containing mixtures; however, they have thus far been unable to meet MIL-PRF-24385(SH) requirements. The purpose of this toxicity assessment is to evaluate the potential toxicities of eight different phosphonate-based polymers for addition to fluorine-free AFFFs in order to help improve performance while reducing environmental and human toxicity concerns.

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1 SUMMARY

1.1 Overview

Research, development, testing, training, and use of substances potentially less hazardous to human health and the environment is vital to the readiness of the Department of Defense (DoD). Safeguarding the health of Warfighters, civilians, and the environment requires an assessment of alternatives before they are fielded. Continuous assessments begun early in the Research, Development, Testing and Evaluation (RDT&E) process can save significant time and effort during RDT&E, as well as over the life cycle of the items developed. Residues of fire suppressants, pyrotechnics, propellants, explosives and incendiaries that were part of mission-essential activities have been found in soil, air, surface and groundwater samples. Remediation of the contaminated areas has cost the DoD millions of dollars and can interfere with training activities. Exposures to these contaminants can lead to long-term health effects. The Toxicity Assessment evaluates and assesses the environmental and occupational health hazards associated with use and demilitarization of phosphorus functional polymer-based fire suppression additives designed to enhance polyfluoroalkyl substances (PFAS)-free fire suppressants for Military use.

1.2 Purpose

The 2020 National Defense Authorization Act (NDAA) has codified the prohibition of the use of aqueous film forming foams (AFFF) containing per and PFAS fire suppressants, effective 1 October 2024. Currently, no facilities are utilizing PFAS-containing AFFF formulations, except those that are capable of collecting effluent prior to environmental exposure. Before this ban goes into effect, multiple facilities are investigating the feasibility of utilizing fluorine-free AFFF as replacements to the fluorine-containing mixtures, which have not yet been able to meet Military Performance Specification (MIL-PRF)-24385(SH) requirements. The purpose of this toxicity assessment is to evaluate the potential toxicities of eight different phosphonate-based polymers for addition to fluorine-free AFFFs in order to help improve performance, meet MIL-PRF-24385(SH) requirements, while also reducing environmental and human toxicity concerns.

1.3 Conclusions

The proposed chemicals for use in PFAS-free AFFF formulations generally have lower predicted persistence, bioaccumulation and toxicity compared to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), two legacy PFAS compounds found at high levels at sites where AFFFs are frequently utilized (Dasu et al. 2022). A full comparison between the proposed polyphosphonate additives and all utilized PFAS in existing AFFF formulations is not feasible due to the large number of potential comparators. PFOA and PFOS were selected to represent PFAS due to the amount of data available on their toxicity. The primary areas of concern with the proposed additives were in the areas of aquatic and oral toxicity. A few additives were predicted to be ocular or inhalational hazards as well.

1.4 Recommendations

Significant data gaps for toxicity and fate and transport exist for many of these materials, predictive modeling was necessary to determine potential toxicities in the absence of empirical data. In order to have a better understanding of the potential toxic effects of these additives, *in vitro* testing is highly recommended for any candidate that is proposed for additional performance assessment by the principal investigator of this project. Proposed methods include genotoxicity, dermal irritation/sensitization, phototoxicity, and acute aquatic toxicity at a minimum. Leading candidates also should have both single and repeat-dose rodent and fish assays conducted to allow for direct comparisons with areas of concern for PFAS. If DEAP is a leading candidate, developmental toxicity assessments should be made.

2 REFERENCES

See Appendix A for list of references. See the Glossary for abbreviations and acronyms.

3 AUTHORITY

Funding for this work was provided under Military Interdepartmental Purchase Request No. 13005002, dated 10 November 2021. This Toxicology Assessment addresses, in part, the environment, safety and occupational health (ESOH) requirements outlined in the following—

- Army Regulation (AR) 200-1, Environmental Protection and Enhancement, (Department of the Army (DA) 2007a);
- AR 40-5, Preventive Medicine, 2007 (DA 2007b);
- AR 70-1, Army Acquisition Policy, 2018 (DA 2018);
- Department of Defense Directive (DoDD) 4715.1E, Environment, Safety, and Occupational Health (ESOH), 2005; Change 1, 2018 (DoD 2018); and
- Army Environmental Requirement and Technology Assessment (AERTA) requirement PP-13-12-03, 2018 (AEC 2018).

The Sponsor is the Strategic Environmental Research and Development Program (SERDP). The Principle Investigator is Dr. Peter Zarras, Naval Air Warfare Center Weapons Division (NAWCWD), China Lake, CA.

4 BACKGROUND

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

In an effort to support this preventive approach, the U.S. Army Public Health Center (APHC) has

been tasked with creating a phased process to identify ESOH effects impacting readiness, training, and development costs. This report represents the status of information available for this work unit as of the date of publication.

5 STATEMENT OF THE PROBLEM

Current fire suppressant formulations utilized by the DoD for extinguishing fuel fires requires the use of PFAS-containing AFFFs. Under the 2020 NDAA, all use of PFAS-containing AFFFs will be banned effective 1 October 2024, due to their long-term human and environmental toxicity concerns (Panieri et al. 2022). Current fluorine-free formulations are not meeting specifications as described in MIL-PRF-24385. The use of phosphorous-containing polymers as a component of PFAS-free AFFFs is under investigation based upon the hypothesis that these polymers will be able to suppress grade F-24 jet fuel or gasoline liquid fires through an “intumescence fire-suppression mechanism,” i.e. smother the fire through rapid expansion upon exposure to the high temperatures found in liquid-fuel based fire (Yan et al. 2012). The use of these polyphosphonate additives is hoped to be more effective than current fluorine-free formulations with fewer long-term environmental and human health consequences.

6 METHODS

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

Table 1. Proposed Compounds

Section	Chemical Substance	CASRN
7.3	Diethyl (2-aminoethyl)phosphonate [DEAP]	41468-36-4
7.4	Diethyl (2-methacrylamidoethyl)phosphonate [DEMAP]	Not registered
7.5	(2-methacrylamidoethyl)phosphonic acid [MAPA]	45028-94-2
7.6	Dihexyl phosphorochloridate [DEPC]	Not registered
7.7	Dihexyl (cyanomethyl)phosphonate [DHCMP]	Not registered
7.8	Dihexyl (2-aminoethyl)phosphonate [DHAEP]	Not registered
7.9	Dihexyl (2-methacrylamidoethyl)phosphonate [DHMAEP]	Not registered
7.10	Didodecyl (2- methacrylamidoethyl)phosphonate [DDMAEP]	Not registered

The physicochemical 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 (^{o}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.

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity and carcinogenicity; and modes and mechanisms of toxicity. Values reported herein include lethal dose 50% (LD_{50}; reported in milligrams (mg) per kilogram (kg) i.e., 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}), 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 (µg/L) or parts per million (ppm). Toxicological information is derived directly from primary sources whenever possible. Sources used in this search included publications from peer-reviewed journals, official government publications and websites, and tertiary reference sources such as *The Merck Index (O'Neil 2006)*. Commercial suppliers may provide results of in-house research that do not appear in the open literature.

In the absence of published information, *in silico* quantitative structure-activity relationship (QSAR) models, such as BIOVIA (BIOVIA 2015), EPI Suites (Estimation Program Interface) (U.S. Environmental Protection Agency (EPA) 2015b), and ECOSAR (Ecological Structure Activity Relationships Predictive Model, Versions 1.11 and 2.0; EPA 2015a) may be used (if applicable to the type of molecule under consideration) to predict toxicity endpoints, physical properties, and ecotoxicity endpoints, respectively.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general categories of risk (i.e., low, moderate, or high) using criteria modified from Howe et al. (Howe et al. 2007). Table B-1 describes the criteria used in the categorization, though the relative proportions of each substance were also factored into the final assessment. In addition, classification in the Globally Harmonized System (GHS) is also included for many of these compounds in Appendix B (UNECE 2015).

7 RESULTS

7.1 Physicochemical Properties

Selected physicochemical properties that are relevant for evaluating toxicity and environmental fate are summarized in Appendix C, Table C-1.

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 Appendix C; Tables C-3, C-4 and C-5, respectively. Each characterization is generally based on the criteria set forth in Table B-1. Where applicable, the GHS categories may be included (see Appendix B 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 Diethyl (2-aminoethyl)phosphonate [DEAP] CASRN 41468-36-4

7.3.1 General Information

DEAP is a clear, odorless liquid. Synonyms include: Diethyl aminoethylphosphonate, 2-diethoxyphosphorylethanamine, Diethyl 2-aminoethylphosphonate, 2-aminoethylphosphonic acid diethyl ester, diethyl(aminoethyl)phosphonate, Phosphonic acid, P-(2-aminoethyl)-, diethyl ester

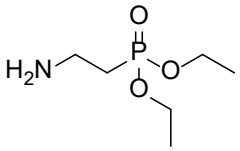

Figure 1. Structure of Diethyl (2-aminoethyl)phosphonate

7.3.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Hazard data were available based off one company report from the European Chemicals Agency (ECHA) Classification and Labelling (C&L) Inventory (ECHA 2020). Where applicable, GHS categories have been applied to the toxicity predictions (UNECE 2015).

7.3.2.1 Oral

The oral LD_{50} in the rat is predicted to be 75.8 mg/kg (GHS category 3) with high confidence. The chronic (1 year) LOAEL is predicted to be 24.1 mg/kg-day (moderate toxicity) with very low confidence. It was reported as GHS Acute Toxicity 4 by ECHA.

7.3.2.2 Inhalation

The oral LC_{50} in the rat is predicted to be 1279.77 mg/m^3-hour (GHS category 3) with high confidence. It was reported at GHS Acute Toxicity 4 by ECHA.

7.3.2.3 Dermal

DEAP is predicted to be a mild skin irritant but is not a skin sensitizer (both with high confidence). ECHA reports DEAP as a GHS category 1B for irritation.

7.3.2.4 Ocular

DEAP is expected to be a severe ocular irritant with high confidence.

7.3.2.5 Development and Reproduction

DEAP is predicted to be a developmental toxicant with high confidence.

7.3.2.6 Genotoxicity

DEAP is predicted to be non-mutagenic in the Ames assay with medium confidence. No other data related to genotoxicity were found.

7.3.2.7 Carcinogenicity

The cancer QSARs consist of multiple individual models based on National Toxicology Program (NTP) and U.S. Food and Drug Administration (FDA) data. DEAP is not a carcinogen by any of the NTP Rodent Carcinogenicity models, however, it is equivocal with the FDA Rodent Carcinogenicity models. Collectively, DEAP is not expected to be carcinogenic.

7.3.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.3.2.9 Mechanism/Mode of Action

No data were found on mode or mechanism of action.

7.3.3 Ecological Data

7.3.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). DEAP is highly soluble (1x 10^6 mg/L) and with a log K_{OC} of 0.6858 it is unlikely to adsorb to soil, thus transport in groundwater is highly likely. A vapor pressure of 0.0101 mmHg indicates that DEAP will exist in the air as vapor, however it is unlikely to volatilize from wet surfaces. The log bioconcentration factor (BCF) of 0.5 and a log K_{OW} of -0.58 indicates that bioaccumulation will not occur.

7.3.3.2 Ecotoxicity

No experimental data were found for DEAP ecotoxicity effects. Both BIOVIA and ECOSAR were

used to estimate the acute aquatic toxicity of DEAP (BIOVIA 2015; EPA 2015a). The chemical did not model well, with EC_{50} predictions ranging from 0.597 mg/L to 2141 mg/L in Daphnia, dependent on chemical class utilized. However, in green algae, all predictions indicated low acute toxicity to DEAP (EC_{50} = 228 – $4x10^6$ mg/L), and in fish, the range was from a GHS 3 to non-toxic range (EC_{50} = 31.6 mg/L – 1955.6 mg/L). Due to the wide range of estimated values and poor model fit, the confidence in these toxicity values is low.

7.3.3.3 Degradation and Treatment

DEAP is expected to be environmentally persistent in sediment, however the majority (93%) will degrade over the course of days to weeks with rapid degradation from air (half-life = 3.6 hours, and moderate degradation from soil (half-life = 720 hours) and water (half-life = 360 hours). It will not be successfully removed in wastewater treatment plants, with 1.76% removed by adsorption to sludge, and 0.9% by biodegradation.

7.4 Diethyl (2-methacrylamidoethyl)phosphonate [DEMAP]

7.4.1 General Information

DEMAP is a light yellow oily substance, with no odor. Synonyms include: N-[2-(diethoxyphosphoryl)-ethyl]methacrylamide, Diethyl [2-(2-methylprop-2-enamido)ethyl]phosphonate.

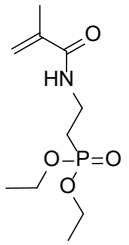

Figure 2. Diethyl (2-methacrylamidoethyl)phosphonate [DEMAP] Structure

7.4.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.4.2.1 Oral

The predicted rat oral for DEMAP is 340.5 mg/kg, with medium confidence. This corresponds to a GHS Category 4. The estimated rat chronic LOAEL is 20.49 mg/kg-day, predicting moderate toxicity at very low confidence.

7.4.2.2 Inhalation

The predicted rat inhalation LC_{50} for DEMAP is 2.5 g/m^3-hour at very low confidence. DEMAP is likely to be a mix of vapor and particulates, and thus is likely to be a GHS category 4 or 5.

7.4.2.3 Dermal

DEMAP is not predicted to be either a dermal irritant or sensitizer at high confidence.

7.4.2.4 Ocular

DEMAP is predicted to be a moderate ocular irritant at high confidence.

7.4.2.5 Development and Reproduction

DEMAP is predicted to not be a developmental toxicant, with high confidence.

7.4.2.6 Genotoxicity

DEMAP is not predicted to be mutagenic in the Ames assay, at very low confidence. No other data about genotoxicity were available.

7.4.2.7 Carcinogenicity

DEMAP is not predicted to be carcinogenic by the NTP rodent carcinogenicity models, it is a mixture of results in the FDA rodent carcinogenicity models. When evaluated together, potential carcinogenicity of DEMAP is equivocal.

7.4.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.4.2.9 Mechanism/Mode of Action

No data were found on the mode/mechanism of action of DEMAP toxicity.

7.4.3 Ecological Data

7.4.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). With an estimated aqueous solubility of 1.43 x 10^4 mg/L and a log K_{OC} of 1.147, it is predicted that DEMAP will be highly soluble and not adsorb to soil and sediment, making it a concern for transport in groundwater. It is unlikely to volatilize from moist surfaces. Due to a vapor pressure of 5.23 x 10^{-6} mmHg, it is likely that DEMAP will be a mixture of vapor and

particulates in air. It is also unlikely to bioaccumulate in the food chain.

7.4.3.2 Ecotoxicity

No ecotoxicity data were found for DEMAP, all predictions are based off of ECOSAR and BIOVIA modeling software (BIOVIA 2015; EPA 2015a). All models predicted moderate toxicity for fish exposed to DEMAP, with an estimated LC_{50} range of 22 – 59 mg/L, corresponding to GHS category 2. In Daphnia, the models were wider, ranging from 0.046 – 864 mg/L for the LC_{50}, spanning all GHS categories for acute aquatic toxicity. A similar result was found for algae, with an LC_{50} range of 0.77 – 5.5 x 10^5 mg/L. This indicates that DEMAP could not be modeled adequately to predict aquatic toxicity with high confidence for aquatic invertebrates and phytoplankton.

7.4.3.3 Degradation and Treatment

DEMAP predominantly partitions to soil and has a biodegradation half-life of 1800 hours (75 days). To a lesser extent, DEMAP partitions to water, with a half-life of 900 hours (37days). Only a small fraction of DEMAP is predicted to enter the atmosphere. Due to photoxidation, the half-life of DEMAP in air is 1.9 hours. This indicates that DEMAP is moderately persistent in the environment. Treatment at waste water treatment facilities will not be effective, with a total predicted removal of 1.85%, 1.76% of that to sludge, the remainder to biodegradation.

7.5 (2-methacrylamidoethyl)phosphonic acid [MAPA] CASRN (45028-94-2)

7.5.1 General Information

MAPA is a solid white compound with no odor. Synonyms include: 2-(Methacryloylamino)ethylphosphonic acid, {2-[(2-Methylacryloyl)amino]ethyl}phosphonic acid

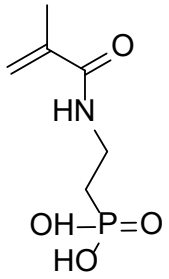

Figure 3. (2-methacrylamidoethyl)phosphonic acid [MAPA] Structure

7.5.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.5.2.1 Oral

The rat acute oral toxicity of MAPA is predicted to be 6788 mg/kg, outside of categorization by GHS, indicating low toxicity. The chronic LOAEL in rats is predicted to be 24.1 mg/kg-day. Both of these are predicted with very low confidence.

7.5.2.2 Inhalation

The inhalation LC_{50} is predicted to be 1914 mg/m^3-hour, which is predicted to be a GHS 4 for dusts/mists. This estimate has very low confidence.

7.5.2.3 Dermal

MAPA is predicted to not cause either dermal irritation or sensitization, with high confidence.

7.5.2.4 Ocular

MAPA is predicted to be a moderate ocular irritant with high confidence.

7.5.2.5 Development and Reproduction

MAPA is predicted to not be a developmental toxicant with high confidence.

7.5.2.6 Genotoxicity

MAPA is not anticipated to be mutagenic in the Ames assay, however this prediction is at very low confidence. No other data on genotoxicity were found.

7.5.2.7 Carcinogenicity

MAPA carcinogen prediction is equivocal. The NTP Rodent assay models were negative for all variables, the FDA rodent assay models were mixed negative and positive, and the weight of evidence (WOE) model was positive.

7.5.2.8 Neurotoxicity

No data on neurotoxicity from MAPA exposure were found.

7.5.2.9 Mechanism/Mode of Action

No data on mechanism or mode of action were found.

7.5.3 Ecological Data

7.5.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). The predicted water solubility of MAPA is very high, at $4.41x10^5$ mg/L. Combined with a low log K_{OC} of 0.378, it is anticipated that MAPA is likely to transport via groundwater but will also adsorb to soils and sediments. In the air, due to a vapor pressure of $5.75 x10^{-9}$ mmHg, MAPA is expected to be sorbed to airborne particulates. With a very low Henry's Law constant of $4.46 x 10^{-18}$ atm-m^3/mol, MAPA is not expected to volatilize from wet surfaces or surface waters. It is unlikely to bioaccumulate, with a log BCF of 0.5 and a log K_{OW} of -1.13.

7.5.3.2 Ecotoxicity

No ecotoxicity data were found, all estimates of toxicity are provided by BIOVIA and ECOSAR (BIOVIA 2015; EPA 2015a). In fish, MAPA is not anticipated to be toxic, with predicted LC_{50} values of 410.18 mg/L in BIOVIA and 2661.3 mg/L in ECOSAR (no GHS category assigned). There may be toxicity in Daphnia , with predicted LC_{50} values of 4.44 mg/L (BIOVIA) and 6534.45 mg/L (ECOSAR), however with this large range, an adequate prediction is not possible with any confidence. The predicted LC_{50} for green algae is 12.89 mg/L, equating to a potential GHS 2 category.

7.5.3.3 Degradation and Treatment

MAPA is expected to be moderately persistent in the environment, with the majority of the compound partitioning to soil and water, with a half-life range of 37-75 days. It will have a rapid rate of air oxidation, with a predicted half-life of 4.3 hours. Sewage treatment at wastewater treatment plants will not be effective due to its low rate of adsorption to soil/sludge and low biodegradability, with a total removal of 1.85% post-treatment, 1.75% of that to sludge.

7.6 Dihexyl phosphorochloridate [DEPC]

7.6.1 General Information

This compound has not yet been synthesized, there are no physical properties available. Synonym: Chloridophosphoric acid dihexyl ester

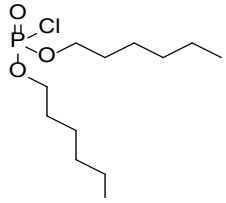

Figure 4. Dihexyl phosphorochloridate [DEPC] Structure

7.6.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been

indicated (UNECE 2015).

7.6.2.1 Oral

The rat oral LD_{50} for DEPC is predicted to be 2744 mg/kg with high confidence. This equates to a GHS 5 categorization for acute oral toxicity. The rat chronic LOAEL is predicted to be 173 mg/kg-day with high confidence.

7.6.2.2 Inhalation

The rat LC_{50} for DEPC is predicted to be 4064 mg/m^3-hour, which equates to a GHS category 4 for acute inhalation toxicity for vapors. This is predicted with very low confidence.

7.6.2.3 Dermal

DEPC is predicted to be a mild skin irritant with high confidence and is not anticipated to be a dermal sensitizer, but with very low confidence.

7.6.2.4 Ocular

DEPC is not anticipated to be an ocular irritant, with high confidence.

7.6.2.5 Development and Reproduction

It is not anticipated that DEPC will be a developmental toxicant, but with very low confidence.

7.6.2.6 Genotoxicity

DEPC is not predicted to be active in the Ames assay, with very low confidence, indicating it is not likely to be mutagenic. No other data with regards to genotoxicity were found.

7.6.2.7 Carcinogenicity

It is not anticipated that DEPC will be carcinogenic. Both the NTP and FDA rodent assay models were mixed, and the WOE model was negative for carcinogenicity.

7.6.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.6.2.9 Mechanism/Mode of Action

No data were found on mechanism or mode of action.

7.6.3 Ecological Data

7.6.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). The relatively low solubility (2 mg/L) and high log K_{OC} of 3.54 indicates that DEPC is unlikely to transport in groundwater, with a higher likelihood of adsorbing to soil and substrate. DEPC is likely to be present in air as a vapor due to a vapor pressure of 1.25x10-4 mmHg and will have slight volatility from wet surfaces. There is a moderate bioaccumulation hazard (log K_{OW} =4.54, log BCF =1.29).

7.6.3.2 Ecotoxicity

No toxicity data were found, so all values are based off BIOVIA and ECOSAR estimates (BIOVIA 2015; EPA 2015a). DEPC in fish is predicted to be a category GHS 1 or 2, with estimated LC_{50}'s of 0.49 to 1.3 mg/L. In Daphnia, it is also expected to be toxic, with an LC_{50} range of 0.026 mg/L to 1.99 mg/L. It is also likely to be toxic in green algae, with an EC_{50} of 0.56 mg/L.

7.6.3.3 Degradation and Treatment

DEPC is biodegradable and susceptible to oxidation, with a half-life of 2.2 hours. DEPC primarily partitions to soil, with an estimated half-life for biodegradation of 720 hours (30 days). It secondarily partitions to water, with an estimated half-life of 360 hours (15 days). It will not be overtly persistent in the environment. Sewage treatment at wastewater treatment plants will be moderately effective, with 57% removal by adsorption to sludge, 0.54% to biodegradation, and 0.3% to air.

7.7 Dihexyl (cyanomethyl)phosphonate [DHCMP]

7.7.1 General Information

This compound has not yet been synthesized, there are no physical properties available. Synonym: 2-dihexoxyphosphorylacetonitrile

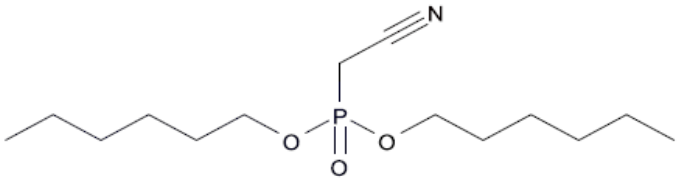

Figure 5. Dihexyl (cyanomethyl)phosphonate [DHCMP] Structure

7.7.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.7.2.1 Oral

The predicted rat oral LD_{50} is 749.8 mg/kg bodyweight, with high confidence. This is a predicted GHS category 4. The rat chronic LOAEL is predicted to be 154.3 mg/kg-day, with very low confidence.

7.7.2.2 Inhalation

The rat LC_{50} is predicted to be 2105 mg/m^3, which is predicted to be either a GHS category 3 or 4 depending on if found as a dust/particulate or a vapor. This is predicted with very low confidence.

7.7.2.3 Dermal

DHCMP is predicted to be a mild irritant but not a skin sensitizer, both with high confidence.

7.7.2.4 Ocular

DHCMP is not anticipated to be an ocular irritant, with high confidence.

7.7.2.5 Development and Reproduction

DHCMP is predicted to not be a developmental toxicant, with high confidence.

7.7.2.6 Genotoxicity

It is not predicted that DHCMP will be active in the Ames mutagenicity assay, with low confidence. No other data were found on additional genotoxicity predictions.

7.7.2.7 Carcinogenicity

It is unlikely that DHCMP will be carcinogenic. All four NTP rodent assay models were negative for carcinogenicity at high confidence, the WOE model was negative, and the FDA rodent carcinogenicity models were mixed.

7.7.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.7.2.9 Mechanism/Mode of Action

No data were found on the mode or mechanism of action.

7.7.3 Ecological Data

7.7.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). DHCMP is predicted to be moderately soluble (10.64 mg/L) and has a moderate predicted log K_{OC} (3.274). Both of these values predict moderate likelihood of transport in water and will also adsorb to soil/sediment. With a predicted vapor pressure of 4.99×10^{-6} mmHg, it is anticipated that DHCMP will exist as both a vapor and a particulate in the air. It is not expected to be overly volatile from moist surfaces, and is moderately likely to bioaccumulate with a log BCF of 1.876 and a log K_{OW} of 3.35.

7.7.3.2 Ecotoxicity

No toxicity data were found, all estimates are made from ECOSAR or BIOVIA models (BIOVIA 2015; EPA 2015a). All models predict that DHCMP will be moderately toxic to fish, with a predicted acute LC_{50} range of 1.6 to 6.3 mg/L, corresponding to GHS category 2. In Daphnia, the LC_{50} range is 0.004 to 0.008 mg/L, corresponding to a GHS category 1. Predictions above the solubility limit were discarded. In algae, the predicted EC_{50} is 3.9 mg/L.

7.7.3.3 Degradation and Treatment

DHCMP is predicted to have limited persistence in the environment, with a predicted biodegradation half-life of 3.9 days to 3 weeks. It primarily partitions to soil, with a soil-specific half-life of 720 hours (30 days). In water, it will degrade over 15 days. It is susceptible to photo-oxidation, with a half-life of 2.2 hours. Sewage treatment will be partly effective, with a total estimated removal of 10.04%, with 9.88% of that to sludge, the remainder to biodegradation.

7.8 Dihexyl (2-aminoethyl)phosphonate [DHAEP]

7.8.1 General Information

This compound has not yet been synthesized, there are no physical properties available. No synonyms were found.

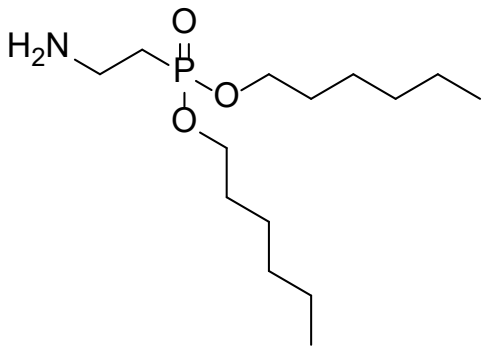

Figure 6. Dihexyl (2-aminoethyl)phosphonate [DHAEP] Structure

7.8.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.8.2.1 Oral

The predicted rat oral LD_{50} for DHAEP is 1061 mg/kg, with very low confidence. This would indicate a GHS 4 categorization. The rat chronic LOAEL is 72.8 mg/kg-day, with very low confidence. This is moderate to low toxicity.

7.8.2.2 Inhalation

It is predicted that the acute LC_{50} for DHAEP is 1504 mg/m^3-hour, which is expected to be a GHS category 3 for vapors.

7.8.2.3 Dermal

DHAEP is expected to be a mild skin irritant with high confidence and is not expected to be a sensitizer with medium confidence.

7.8.2.4 Ocular

DHAEP is not anticipated to be an ocular irritant, at very low confidence.

7.8.2.5 Development and Reproduction

DHAEP is predicted to not be a developmental toxicant with high confidence.

7.8.2.6 Genotoxicity

DHAEP is predicted to not be mutagenic in the Ames assay, with very low confidence. No other data were found regarding genotoxicity potential.

7.8.2.7 Carcinogenicity

DHAEP is not predicted to be carcinogenic with the majority of the NTP rodent, FDA rodent and WOE models predicting a negative result (non-carcinogenic).

7.8.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.8.2.9 Mechanism/Mode of Action

No data were found on mechanism or mode of action.

7.8.3 Ecological Data

7.8.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). DHAEP has moderate aqueous solubility at 189.8 mg/L, this combined with a moderate log K_{OC} of 2.86, indicates that DHAEP will have a moderate to low likelihood of transport in groundwater, and will have moderate adsorption to soil. It will exist in the air as a vapor and is not expected to have any volatility from moist surfaces. It is moderately likely to bioaccumulate, with a log BCF of 1.874 and a log K_{OW} of 3.35.

7.8.3.2 Ecotoxicity

No toxicity data could be found in the literature search, all prediction are based off of BIOVIA or ECOSAR modeling (BIOVIA 2015; EPA 2015a). The LC_{50} in fish is predicted to be between 2.2 and 7.5 mg/L for all models, predicting a GHS category 2 for acute aquatic toxicity. In the Daphnia, the range for the LC_{50} is 0.0196 – 11.56 mg/L, which spans all three acute aquatic GHS categories. Similarly, for green algae, the predicted EC_{50} spans a range from 0.621 to 140.5 mg/L. Aquatic toxicity for invertebrates and phytoplankton cannot be reliably estimated with any confidence based on these models.

7.8.3.3 Degradation and Treatment

DHAEP is likely to biodegrade, with a predicted degradation period of days to weeks. It primarily partitions to soil, followed by water, and then sediment. It will biodegrade in 15-30 days from soil and water, however it will be more persistent in sediment, with a half-life of 135 days. It will be rapidly degraded by oxidation in the air, with a half-life of 1.41 hours. Sewage treatment at wastewater treatment plants will be slightly effective, with a total predicted removal of 10.04%, with 9.88% of that to sludge and the remainder to biodegradation.

7.9 Dihexyl (2-methacrylamidoethyl)phosphonate [DHMAEP]

7.9.1 General Information

This compound has not yet been synthesized, there are no physical properties available. No known synonyms.

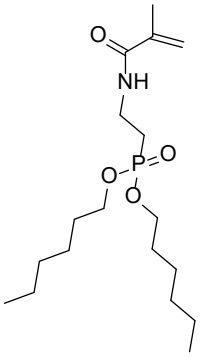

Figure 7. Dihexyl (2-methacrylamidoethyl)phosphonate [DHMAEP] Structure

7.9.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.9.2.1 Oral

The acute oral LD_{50} in the rat is predicted to be 3294 mg/kg, which corresponds to GHS category 5. The chronic LOAEL in the rat is predicted to be 44.6 mg/kg-day. Both of these are predicted at very low confidence.

7.9.2.2 Inhalation

The acute inhalation LC_{50} is predicted to be 2.66 g/m^3-hour, which corresponds to a GHS category 5 for acute inhalation of a dust or mist. This prediction is at very low confidence.

7.9.2.3 Dermal

DHMAEP is predicted to be a mild skin irritant and not a skin sensitizer, both with low confidence.

7.9.2.4 Ocular

DHMAEP is not expected to be an ocular irritant, at low confidence.

7.9.2.5 Development and Reproduction

DHMAEP is not expected to be a developmental toxicant at medium confidence.

7.9.2.6 Genotoxicity

DHMAEP was modeled as negative in the Ames mutagenicity assay; however, the confidence

in this score is so low that this result is deemed unreliable. No other data related to genotoxicity were found.

7.9.2.7 Carcinogenicity

DHMAEP is not predicted to be a carcinogen, at low confidence.

7.9.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.9.2.9 Mechanism/Mode of Action

No data were found on mechanism or mode of action.

7.9.3 Ecological Data

7.9.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). Aqueous solubility for DHMAEP is relatively low at 1.394 mg/L, combined with a log K_{OC} of 3.32, DHMAEP is not likely to transport in groundwater due to a moderate likelihood of adsorption to soils and sediment. With a vapor pressure of $2.35x10^{-8}$, it will exist mostly as particulate in the air. It is non-volatile and has a low to moderate likelihood of bioaccumulation with a log BCF of 1.057 and a log K_{OW} of 4.19.

7.9.3.2 Ecotoxicity

No toxicity data were found, all estimations were made utilizing either BIOVIA or ECOSAR models (BIOVIA 2015; EPA 2015a). The models all predicted moderate to high toxicity in algae, Daphnia, and fish, with a caveat that anything above the solubility limit of 1.394 mg/L was very low confidence and should be discarded. The majority of the models did qualify DHMAEP as high toxicity for all three model species with predicted EC_{50} at or below 1 mg/L, making DHMAEP a GHS category 1 for aquatic toxicity.

7.9.3.3 Degradation and Treatment

Biodegradation is expected to take days to weeks, indicating that DHMAEP is biodegradable. It primarily partitions to soil, followed by water and then sediment. It will degrade from soil and water in 15-30 days, but will persist in sediment for approximately 135 days. Sedimentary partitioning accounts for 3.2% of DHMAEP in the environment. It is rapidly oxidized in the air, with a half-life of 1.4 hours. Sewage treatment will be moderately effective in wastewater treatment plants, with 39.41% removal following treatment, 39.02% of that to sludge, the remainder to biodegradation.

7.10 Didodecyl (2- methacrylamidoethyl)phosphonate [DDMAEP]

7.10.1 General Information

This compound has not yet been synthesized, there are no physical properties available. No synonyms were found.

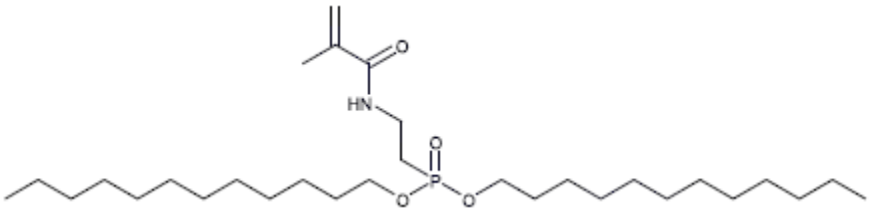

Figure 8. Didodecyl (2- methacrylamidoethyl)phosphonate [DDMAEP] Structure

7.10.2 Toxicology Data

No toxicity data were found in the literature, all toxicity estimations are calculated from the use of BIOVIA modeling software (BIOVIA 2015). Where applicable, GHS categories have been indicated (UNECE 2015).

7.10.2.1 Oral

BIOVIA predicts that DDMAEP will have low acute oral toxicity in the rat, with a predicted LD_{50} of 9735 mg/kg, but with very low confidence. The predicted chronic LOAEL is 34.5 mg/kg-day, also with very low confidence.

7.10.2.2 Inhalation

The LC_{50} in rats is predicted to be 0.471 g/m^3-hour, with very low confidence. This equates to GHS category 2 for acute inhalation.

7.10.2.3 Dermal

DDMAEP is predicted to be a mild irritant with very low confidence, and is not expected to be a skin sensitizer, again with very low confidence.

7.10.2.4 Ocular

It is not anticipated that DDMAEP will be an ocular irritant, with very low confidence.

7.10.2.5 Development and Reproduction

DDMAEP did not model as a developmental toxicant, again with very low confidence.

7.10.2.6 Genotoxicity

DDMAEP is not expected to be a mutagen, and was predicted to be negative in the model for Ames mutagenicity with very low confidence. No other data on genotoxicity were found.

7.10.2.7 Carcinogenicity

DDMAEP is not expected to be carcinogenic with very low confidence.

7.10.2.8 Neurotoxicity

No data were found on neurotoxicity.

7.10.2.9 Mechanism/Mode of Action

No data were found on the mechanism or mode of action.

7.10.3 Ecological Data

7.10.3.1 Fate and Transport

No data were found. All physical-chemical parameters were modeled with EPI Suites (EPA 2015b). DDMAEP has very low predicted aqueous solubility ($1.13x10^{-6}$ mg/L) and a large predicted log K_{OC} (6.578), so is not expected to transport in groundwater, but is highly likely to adsorb to soil and other surfaces. With a predicted vapor pressure of $2.06x10^{-8}$ mmHg, DDMAEP is predicted to exist as a mix of vapor and particulates. It is also predicted to bioaccumulate, with a log BCF of 2.017 and a log K_{OW} of 10.08.

7.10.3.2 Ecotoxicity

Modeling DDMAEP for toxicity with both ECOSAR and BIOVIA resulted in predictions of very high ecotoxicity for the species modeled (BIOVIA 2015; EPA 2015a). The LC_{50} in fish, Daphnia, and algae were all predicted to be less than 0.02 mg/L. This equates to a GHS category 1 for acute aquatic toxicity.

7.10.3.3 Degradation and Treatment

DDMAEP is predicted to be moderately persistent. It will primarily partition to soil, with a degradation half-life of 75 days, the remainder will go to water and sediment, where sediment has a prolonged half-life of 337 days. It is predicted to have 94.04% removal by treatment at wastewater treatment plants, the majority of which is by adsorption to sludge (93.26%), with the remainder to biodegradation.

8 DISCUSSION

8.1 Compound Summaries

8.1.1 DEAP

No experimental data were found regarding DEAP toxicity. DEAP is not expected to be overtly acutely toxic, however it is predicted to be both a dermal and an ocular irritant. It is also expected to be a developmental toxicant. Its high solubility and predicted moderate environmental persistence would indicate that it may be a release hazard from production facilities, however it is unlikely to be toxic to aquatic wildlife. Releases should be controlled and appropriate personal protective equipment (PPE) should be worn when working with DEAP. It is recommended that basic *in vitro* toxicity screening be conducted, inclusive of the Ames mutagenicity assay, skin sensitization and irritation, photolytic potential, and aquatic toxicity assessments. The potential for developmental toxicity should also be further explored.

8.1.2 DEMAP

No experimental data were found regarding DEMAP toxicity. It was not predicted to have high acute toxicity. However, DEMAP is predicted to be a moderate ocular irritant. DEMAP has very high predicted solubility and moderate environmental persistence, and is a release concern for areas surrounding manufacturing facilities. Due to these occupational and environmental factors, appropriate PPE should be worn until more comprehensive toxicity data can be produced, and releases into the environment should be limited, due to potential for toxic effects in aquatic species. It is recommended that *in vitro* screening be conducted on DEMAP, inclusive of genotoxicity, dermal irritation and sensitization, aquatic toxicity, and photolytic potential. Additional acute and repeat-dose rodent assays may be necessary as well.

8.1.3 MAPA

MAPA is not anticipated to be toxic to human health or the environment. It does have potential to be transported in groundwater and will be moderately environmentally persistent, so release into the environment should be minimized. Until toxicological assessments can occur, appropriate PPE should be worn to mitigate any unknown toxic effects. At a minimum, an *in vitro* assessment to include the Ames mutagenicity assay, dermal irritation and sensitization, aquatic toxicity, and phototoxicity for photolytic effects should be conducted. Follow-on acute and repeat dose rodent assays may be necessary as well.

8.1.4 DEPC

DEPC does not appear to have high toxicity concerns terrestrial vertebrates, however it does appear to be highly toxic to aquatic species. It is unlikely to transport in groundwater, so the highest area of concern is near the area of release if released. It is predicted to be a mild irritant, so appropriate PPE is recommended. To confirm the potential toxicity concerns for DEPC, standard *in vitro* screens should be conducted, to include the Ames mutagenicity assay, dermal irritation and sensitization assays, photolytic potential, and aquatic toxicity at a minimum. Assessment for *in vivo* toxicity may also need to be conducted.

8.1.5 DHCMP

DHCMP is expected to be mild to moderately toxic following both oral and inhalational exposures. It is predicted to be a mild skin irritant. Appropriate PPE should be worn at all times with this chemical. Environmental releases should be minimized due to the potential for aquatic toxicity and transport in the groundwater. Basic *in vitro* testing should be performed, inclusive on genotoxicity, aquatic toxicity, dermal irritation and sensitization, and photolytic potential. Additional single and repeat-dose rodent assays may be recommended.

8.1.6 DHAEP

DHAEP is predicted to have at most moderate acute toxicity to vertebrates and invertebrates. It is likely to both transport in groundwater and adsorb to soil and sediment, so releases into the environment should be well controlled. It is predicted to be a mild irritant, so appropriate PPE is recommended. A basic screening battery for mutagenicity, dermal irritation and sensitization, aquatic toxicity, and phototoxicity (photolysis) should be conducted to better understand the likelihood of toxicity. Additional acute oral and repeat dose rodent assays may be added eventually if necessary.

8.1.7 DHMAEP

The primary toxicity and exposure concerns with DHMAEP are aquatic toxicity effects and inhalational exposures. There is a mild concern with skin irritation following exposure. Appropriate PPE should be worn and releases from processing plants limited until further characterization of the toxicity can be conducted. Suggested toxicity testing includes a basic *in vitro* screen for mutagenicity, dermal toxicity, phototoxicity and aquatic toxicity. Additionally, an acute inhalation and oral assessment in rodents should be conducted at a minimum, with the potential for additional repeat-dose studies.

8.1.8 DDMAEP

DDMAEP is likely to be an acute inhalation hazard and there is potential for mild skin irritation upon exposure. Appropriate PPE should be worn when working with the compound. It is expected to have very high toxicity in aquatic environments, and releases into the environment should be limited. However due to the fact that it will adsorb to soil, it is unlikely to transport in water and will not be a concern for groundwater contamination beyond the immediate release site. In order to better characterize the toxicity, which was all predicted with very low confidence in the models, a basic *in vitro* toxicity screen should be conducted (Ames, dermal sensitization and irritation, phototoxicity, aquatic toxicity to include bacterial luminescence and Daphnia at a minimum), along with an acute oral and inhalation rat assay, with the potential for a repeat dose assay.

8.2 Regulations and Standards

8.2.1 DEAP

No regulations or standards were found. DEAP is predicted to be a GHS category 3 for acute toxicity and a category 5 for inhalation by BIOVIA modeling (UNECE 2015). PubChem predicted that DEAP is a category 4 chemical for acute toxicity and a 1B for skin corrosion (PubChem 2022).

8.2.2 DEMAP

No standards or regulations were found. The predicted acute oral GHS category is category 4 while the predicted acute inhalation GHS category is category 4 or 5 (UNECE 2015). For ocular irritation, the predicted GHS category likely corresponds to GHS category 2A.

8.2.3 MAPA

MAPA is not anticipated to be toxic to vertebrates, with a predicted GHS category of 4 for inhalation and no categorization for oral toxicity (UNECE 2015). MAPA also will likely be at most a GHS category 2 for aquatic toxicity, particularly for invertebrates.

8.2.4 DEPC

No regulations or standards were found, however DEPC is likely to have low toxicity (GHS category 4 or 5) for acute mammalian toxicity (UNECE 2015). However, it is likely that DEPC is highly toxic to aquatic species, with a predicated GHS category 1 or 2.

8.2.5 DHCMP

No regulations or standards were found. Acute oral toxicity is predicted to be a GHS category 4, while acute inhalation toxicity is either a GHS 3 or 4 (UNECE 2015). The aquatic toxicity GHS category is either 1 or 2 depending on the organism. DHCMP is a category 3 for skin irritation.

8.2.6 DHAEP

No regulations or standards were found. DHAEP is predicted to have low to moderate acute toxicity, with predicted GHS categories of 3 and 4 for inhalation and oral toxicity respectively (UNECE 2015). DHAEP is likely to be moderately toxic to aquatic species with a predicted GHS category 2. With a prediction of mild irritation, it is predicted to be a GHS category 3.

8.2.7 DHMAEP

No regulations or standards were found for DHMAEP. The compound is predicted to be GHS category 5 for acute oral toxicity and category 3 for acute inhalation toxicity (UNECE 2015). As a mild irritant, it would be predicted to be a GHS category 3. For aquatic toxicity, it is predicted to be a GHS category 1.

8.2.8 DDMAEP

No regulations or standards were found. DDMAEP is predicted to be a GHS category 2 for acute inhalation and a category 1 for aquatic toxicity (UNECE 2015). In terms of occupational concerns, DDMAEP is predicted to be a GHS category 3 for dermal irritation.

9 RECOMMENDATIONS

The proposed chemicals for use in PFAS-free AFFF formulations generally have lower predicted toxicity as compared to PFOA and PFOS, two legacy PFAS compounds. A full comparison between the proposed polyphosphonate additives and all utilized PFAS in existing AFFF formulations is not feasible due to the large number of potential comparators. PFOA and PFOS were selected due to the amount of data available on their toxicity.

These phosphorus-based compounds are not expected to be persistent or bioaccumulate in biota similar to PFAS-containing AFFF; however, there are indications of persistence and bioaccumulation concerns for DEPC and DDMAEP, respectively. The breakdown and liberation of phosphorus could result in nutrification of waterways and encourage algal blooms, which can reduce oxygen content and result in acute stress to fish and aquatic organisms. This requires high releases to waterways; therefore, efforts to reduce significant releases to receiving surface waterways is recommended.

In order to have a better understanding of the potential toxic effects of these additives, *in vitro* testing is highly recommended for any candidate that is proposed for additional performance assessment by the principal investigator of this project. Proposed methods include genotoxicity, dermal irritation/sensitization, phototoxicity, and acute aquatic toxicity at a minimum. Leading candidates also should have both single and repeat-dose rodent and fish assays conducted to allow for direct comparisons with areas of concern for PFAS. If DEAP is a leading candidate, developmental toxicity assessments should be made. Similar to the perfluorinated compounds, there appears to be a direct relationship between toxicity and carbon-chain length for the chemicals evaluated in this report (De Silva et al. 2021). While an in depth analysis of these potential issues is not possible here, the effects of carbon chain length on toxicity and bioavailability should be fully characterized for the WP-3235 compounds. Table 2 provides a summary of human health and ecological concerns with each of the assessment compounds and representative chemicals they are proposed to replace.

Table 2: Human Health and Ecological Assessment

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]
PFOA	4† H302†	4† H332†	1B†	1† H318†	2† H351†	3†4 H412†	P	BA	STOT† RE1† RT† 1B† H372† H360D† H362†	RT[5]	PBT†, POP†	P	PBT†
PFOS	4† H302†	4† H332†	1B† H314†	1† H318†	2† H351†	2†4 H411†	P	BA	STOT† RE 1† RT 1B† H372† H360† H362†	RT[5]	P	P	P
DEAP	P	P	P	P	P	P			P; DT		P	P	P
DEMAP	P	P	P	P	P	P			P		P	P	P
MAPA	P	P	P	P	P	P			P		P	P	P
DEPC	P	P	P	P	P	P			P		P	P	P
DHCMP	P	P	P	P	P	P			P		P	P	P
DHAEP	P	P	P	P	P	P			P		P	P	P
DHMAEP	P	P	P	P	P	P			P		P	P	P
DDMAEP	P	P	P	P	P	P			P		P	P	P

Notes:
*Annotated with key hazards and critical endpoints. See Appendix B for further information on the hazard codes and color schemes.
† ECHA, 2022
[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.
=unknown toxicity
[4] Chronic toxicity
[5] (Dennis et al. 2021)
BA/C=bio-accumulates/concentrates
DT = developmental toxicant
G=genotoxic
NT=neurotoxicant
P=predicted based on *in silico* data, read-across, and expert opinion
PFOA = perfluorooctanoic acid
PFOS = perfluorooctane sulfonic acid
RT=reproductive toxicant
PBT = Persistent, bioaccumulative and toxic
POP = Persistent organic pollutant
STOT = specific targeted organ toxicity

10 POINT OF CONTACT

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Michael J. Quinn, Ph.D. Date
Division Chief,
Health Effects Research Program

JOHNSON.MARK.STEVEN.1229380717 Digitally signed by JOHNSON.MARK.STEVEN.1229380717 Date: 2022.05.26 10:59:04 -04'00'

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

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[a]

	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. 10–1000 mg/L log K_{OC} 2.0–1.0	Water sol. > 1000 mg/L log K_{OC} <1.0	
BIOACCUMULATION	log K_{OW} <3.0	log K_{OW} 3.0–4.5	log K_{OW} >4.5	
TOXICITY	No evidence of carcinogenicity/ Mutagenicity (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 (IARC group 1 & 2A)/ mutagenicity; 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
K_{OC} = soil organic carbon-water partitioning coefficient
K_{OW} = octanol-water partition coefficient
IARC = International Agency for Research on Cancer
mg/kg-d = milligrams per kilogram per day
LOAEL = lowest-observed adverse effect level
LC_{50} = median lethal concentration; concentration expected to result in 50% mortality to a population of test animals
LD_{50} = median lethal dose; dose resulting in 50% mortality
EC_{50} = half maximal effective concentration
µg/L = micrograms per liter
Note:
[a]Modified from Howe, et al. (Howe 2007)

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; creating a classification process for comparison with defined hazard criteria; and communicating hazard information and protective measures on labels and Safety Data Sheets (SDS, formerly known as Material Safety Data Sheets). 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 one most important area for our purposes is classification of chemicals into various hazard categories based upon their effects and the route of exposure. Tabular extracts of the criteria for acute toxicity (both oral and inhalation), dermal, and ocular effects are included below. More information can be found in the original source (OSHA 2012).

Table B-2. GHS Acute Toxicity

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

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

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.

Table B-7. Hazard Code Table

Code	Hazard Statements	Hazard Class	Category	Signal Word
H300	Fatal if swallowed	Acute toxicity, oral	Category 1, 2	Danger
H301	Toxic if swallowed	Acute toxicity, oral	Category 3	Danger
H302	Harmful if swallowed	Acute toxicity, oral	Category 4	Warning
H303	May be harmful if swallowed	Acute toxicity, oral	Category 5	Warning
H304	May be fatal if swallowed and enters airways	Aspiration hazard	Category 1	Danger
H305	May be fatal if swallowed and enters airways	Aspiration hazard	Category 2	Warning
H310	Fatal in contact with skin	Acute toxicity, dermal	Category 1, 2	Danger
H311	Toxic in contact with skin	Acute toxicity, dermal	Category 3	Danger
H312	Harmful in contact with skin	Acute toxicity, dermal	Category 4	Warning
H313	May be harmful in contact with skin	Acute toxicity, dermal	Category 5	
H314	Causes severe skin burns and eye damage	Skin corrosion/irritation	Category 1A, 1B, 1C	Danger
H315	Causes skin irritation	Skin corrosion/irritation	Category 2	Warning
H316	Causes mild skin irritation	Skin corrosion/irritation	Category 3	Warning
H317	May cause an allergic skin reaction	Sensitization, Skin	Category 1, 1A, 1B	Warning
H318	Causes serious eye damage	Serious eye damage/eye irritation	Category 1	Danger
H319	Causes serious eye irritation	Serious eye damage/eye irritation	Category 2A	Warning
H320	Causes eye irritation	Serious eye damage/eye irritation	Category 2B	Warning
H330	Fatal if inhaled	Acute toxicity, inhalation	Category 1, 2	Danger
H331	Toxic if inhaled	Acute toxicity, inhalation	Category 3	Danger
H332	Harmful if inhaled	Acute toxicity, inhalation	Category 4	Warning
H333	May be harmful if inhaled	Acute toxicity, inhalation	Category 5	Warning
H334	May cause allergy or asthma symptoms or breathing difficulties if inhaled	Sensitization, respiratory	Category 1, 1A, 1B	Danger
H335	May cause respiratory irritation	Specific target organ toxicity, single exposure; Respiratory tract irritation	Category 3	Warning
H336	May cause drowsiness or dizziness	Specific target organ toxicity, single exposure; Narcotic effects	Category 3	Warning

Table B-7. Hazard Code Table, continued

Code	Hazard Statements	Hazard Class	Category	Signal Word
H340	May cause genetic defects	Germ cell mutagenicity	Category 1A, 1B	Danger
H341	Suspected of causing genetic defects	Germ cell mutagenicity	Category 2	Warning
H350	May cause cancer	Carcinogenicity	Category 1A, 1B	Danger
H350i	May cause cancer by inhalation	Carcinogenicity	Category 1A, 1B	Danger
H351	Suspected of causing cancer	Carcinogenicity	Category 2	Warning
H360	May damage fertility or the unborn child	Reproductive toxicity	Category 1A, 1B	Danger
H360F	May damage fertility	Reproductive toxicity	Category 1A, 1B	Danger
H360D	May damage the unborn child	Reproductive toxicity	Category 1A, 1B	Danger
H360FD	May damage fertility; May damage the unborn child	Reproductive toxicity	Category 1A, 1B	Danger
H360Fd	May damage fertility; Suspected of damaging the unborn child	Reproductive toxicity	Category 1A, 1B	Danger
H360Df	May damage the unborn child; Suspected of damaging fertility	Reproductive toxicity	Category 1A, 1B	Danger
H361	Suspected of damaging fertility or the unborn child	Reproductive toxicity	Category 2	Warning
H361f	Suspected of damaging fertility	Reproductive toxicity	Category 2	Warning
H361d	Suspected of damaging the unborn child	Reproductive toxicity	Category 2	Warning
H361fd	Suspected of damaging fertility; Suspected of damaging the unborn child	Reproductive toxicity	Category 2	Warning
H362	May cause harm to breast-fed children	Reproductive toxicity, effects on or via lactation	Additional category	
H370	Causes damage to organs	Specific target organ toxicity, single exposure	Category 1	Danger
H371	May cause damage to organs	Specific target organ toxicity, single exposure	Category 2	Warning
H372	Causes damage to organs through prolonged or repeated exposure	Specific target organ toxicity, repeated exposure	Category 1	Danger
H373	Causes damage to organs through prolonged or repeated exposure	Specific target organ toxicity, repeated exposure	Category 2	Warning
H400	Very toxic to aquatic life	Hazardous to the aquatic environment, acute hazard	Category 1	Warning
H401	Toxic to aquatic life	Hazardous to the aquatic environment, acute hazard	Category 2	
H402	Harmful to aquatic life	Hazardous to the aquatic environment, acute hazard	Category 3	
H410	Very toxic to aquatic life with long lasting effects	Hazardous to the aquatic environment, long-term hazard	Category 1	Warning
H411	Toxic to aquatic life with long lasting effects	Hazardous to the aquatic environment, long-term hazard	Category 2	
H412	Harmful to aquatic life with long lasting effects	Hazardous to the aquatic environment, long-term hazard	Category 3	
H413	May cause long lasting harmful effects to aquatic life	Hazardous to the aquatic environment, long-term hazard	Category 4	
H420	Harms public health and the environment by destroying ozone in the upper atmosphere	Hazardous to the ozone layer	Category 1	Warning

APPENDIX C

DATA TABLES

Table C-1. Physical and Chemical Properties: sources EPISuites (2015)

Compound	Molar Mass (g/mol)	Melting Point (ºC)	Boiling Point (ºC)	Aqueous solubility (mg/L) @ 25ºC	log K_{OW}	log K_{OC}	Henry's Law Constant (atm-m^3/mol) @ 25ºC	Vapor Pressure mmHg @ 25°C
PFOA*	414.07	27.28	203.77	0.0021	4.81	2.816	9.08E-2	0.145
PFOS*	500.13	51.9	229.28	0.1039	4.49	3.409	1.1E-2	0.0064
DEAP	181.17	42.35	261.67	1E6	-0.58	0.6858	3.01E-10	0.0101
DEMAP	249.24	84.03	384.99	1.43E+04	0.26	1.147	8.05E-13	5.23E-06
MAPA	193.14	84.28	418.44	4.41E+05	-1.13	0.378	4.46E-18	5.75E-9
DEPC	284.76	70.28	332.89	2.002	4.54	3.54	1.40E-05	0.000125
DHCMP	289.351	84.15	385.76	10.64	3.35	3.274	8.81E-09	4.99E-06
DHAEP	293.39	88.68	369.97	189.8	3.35	2.86	2.90E-09	1.43E-03
DHMAEP	361.47	90.06	477.82	1.394	4.19	3.32	7.77E-12	2.35E-08
DDMAEP	529.79	90.27	480	1.13E-06	10.08	6.578	2.33E-10	2.06E-08

Legend:
*PFOA and PFOS were modeled for the purposes of comparing how the models perform for a persistent organic pollutant
g/mol = grams per mole
mg/L = milligrams per liter
atm-m^3/mol = air to mol per cubic meter

Table C-2. Toxicity Data (BIOVIA, 2015)

Compound	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Development/ Reproduction	Genotoxicity	Carcinogenicity
DEAP	75.8	24.1	1.279	Mild irritant, negative sensitization	Severe irritant	Positive	Negative	Negative
DEMAP	340.5	20.5	2.5	Negative	Moderate	Negative	Negative	Negative
MAPA	6788.9	24.85	1.915	Negative	Moderate Irritant	Negative	Negative	Negative
DEPC	2744	172.98	4.065	Mild irritant	Negative	Negative	Negative	Negative
DHCMP	749.8	154.3	2.1	Mild irritant	Negative	Negative	Negative	Negative
DHAEP	1060.5	72.8	1.5	Mild irritant	Negative	Negative	Negative	Negative
DHMAEP	3294	44.6	2.66	Mild irritant	Negative	Negative	Negative	Negative
DDMAEP	9735	34.5	0.470	Mild irritant	None	Negative	Negative	Negative

Legend:
mg/kg = milligrams per kilograms
mg/kg-d = milligrams per kilograms per day
g/m^3-h = grams per cubic meter per hour

Table C-3. Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
DEAP	Moderate	Moderate	Moderate	High	Low	
DEMAP	Moderate	Low	Low	Moderate	Low	
MAPA	Moderate	Low	Low	Moderate	Low	
DEPC	Low	Low	Moderate	Low	Low	
DHCMP	Moderate	Moderate	Moderate	Low	Low	
DHAEP	Moderate	Low	Low	Low	Low	
DHMAEP	Moderate	Moderate	Moderate	Low	Low	
DDMAEP	Moderate	High	Moderate	Low	Low	

Table C-4. *In Silico* Aquatic Ecotoxicity Data

		BIOVIA QSAR		ECOSAR			
Compound	**solubility (mg/L)**	**Daphnid EC_{50} (mg/L)**	**Fish LC_{50} (mg/L)**	**ECOSAR Model Class**	**Green Algae EC_{50} (mg/L)**	**Daphnid LC_{50} (mg/L)**	**Fish LC_{50} (mg/L)**
DEAP	1.00E+06	0.597	1955.6	Aliphatic amines	228.6	152.9	1732.6
				Esters	1372	2141.1	781.1
				Esters (phosphate)	4E+06	0.07	31.6
DEMAP	1.43E+04	31.7	0.192	Esters	484.7	864.7	37.4
				Esters (phosphate)	5.8E+05**	0.046	22.01
				Acrylamides	0.78	151.4	59.1
MAPA	4.41E+05	4.44	410.18	Acrylamides(acid)	12.9	6534.5	2661.3
DEPC	2.002	0.026	0.49	Esters	0.57	2.0	1.3
				Esters (phosphate)	5.12*	0.00123	0.80
				Acid Halides	2.012*	1.2	1.02
DHCMP	10.64	0.008	1.6	Esters	3.91	11.4*	6.3
				Esters (phosphate)	137.9**	0.004	2.1
DHAEP	189.8	0.0196	4.42	Aliphatic amines	0.62	1.03	7.4
				Esters	3.98	11.56	6.4
				Esters (phosphate)	140.54	0.004	2.2
DHMAEP	1.394	0.0038	0.064	Esters	1.26	4.18*	2.542*
				Esters (phosphate)	16.96**	0.002	1.34
				Acrylamides	0.130	1.740*	0.60
DDMAEP	1.13E-06	1.6E-05	6.12E-6	Esters	0.00139**	0.00118**	0.0014*
				Esters (phosphate)	2.3E-06	1.77E-05	0.017**
				Acrylamides	0.008**	0.0018**	0.00058**

*Predicted toxicities above the solubility limit of compound; ** exceeds water solubility by 10-fold = no effects at saturation.

Table C-5. Ecotoxicity Assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
DEAP	Low	Unk	Unk	Moderate	Unk	
DEMAP	Moderate	Unk	Unk	Moderate	Unk	
MAPA	Moderate	Unk	Unk	Moderate	Unk	
DEPC	High	Unk	Unk	Low	Unk	
DHCMP	High	Unk	Unk	Moderate	Unk	
DHAEP	Moderate	Unk	Unk	Moderate	Unk	
DHMAEP	High	Unk	Unk	Moderate	Unk	
DDMAEP	High	Unk	Unk	Moderate	Unk	

GLOSSARY

AEC	Army Environmental Command
AERTA	Army Environmental Research and Technology Assessment
AFFF	aqueous film forming foams
APHC	U.S. Army Public Health Center
AR	Department of the Army Regulation
atm	atmosphere
BCF	bioconcentration factor
BP	boiling point
C&L	Classification and Labelling
CASRN	Chemical Abstracts Service Registry Number
ºC	degrees Celsius
DA	Department of the Army
dL	deciliter
DDMAEP	Didodecyl (2- methacrylamidoethyl)phosphonate
DEAP	Diethyl (2-aminoethyl)phosphonate
DEMAP	Diethyl (2-methacrylamidoethyl)phosphonate
DEPC	Dihexyl phosphorochloridate
DHAEP	Dihexyl (2-aminoethyl)phosphonate
DHCMP	Dihexyl (cyanomethyl)phosphonate
DHMAEP	Dihexyl (2-methacrylamidoethyl)phosphonate
DoD	Department of Defense
DoDD	Department of Defense Directive
ECHA	European Chemicals Agency
ECOSAR	Ecological Structure Activity Relationship
EC	Effect concentration

EC_{50}	median (50%) effect concentration
EPA	U.S. Environmental Protection Agency
ESOH	Environmental safety and occupational health
FDA	U.S. Food and Drug Administration
GHS	Global Harmonization System
Cat	Category
g	Grams
g/m^3-h	Grams/cubic meter per hour
K_H	Henry's law constant
IC_{50}	median (50%) inhibitory concentration
kg	kilogram
L	liter
LC_{50}	median (50%) lethal concentration
LD_{50}	median (50%) lethal (oral) dose
log K_{OC}	Log Organic carbon partition coefficient
log K_{OW}	Log Octanol-water partition coefficient
LOAEL	lowest-observed adverse effect level
MAPA	(2-methacrylamidoethyl)phosphonic acid
MP	melting point
µg	micrograms
µL	microliter
µM	micromolar
MIL-PRF	Military Performance Specification
m^3	cubic meter
mg	milligram
mL	milliliter

mmHg	millimeter of mercury
mM	millimolar
mol	mole
MW	molecular weight
NAWCWD	Naval Air Warefare Center Weapons Division
NDAA	National Defense Authorization Act
NOAEL	no-observed adverse effect level
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PFAS	per and polyfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PPE	Personal Protective Equipment
PPM	parts per million
QSAR	Quantitative Structure-Activity Relationship
RDT&E	research, development, testing, and evaluation
RfD	reference dose
SDS	safety data sheets
SERDP	DoD Strategic Environmental Research and Development Program
TOX	Toxicology Directorate
UNECE	United Nations Economic Commission for Europe
VP	vapor pressure
w/v	weight per volume