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Toxicology Directorate

Toxicology Assessment for Department of Defense Strategic Environmental Research and Development (SERDP) Project WP-2601: Sustainable Environmentally Green Polyurethanes for Erosion-Resistant Coatings, March 2016–June 2018

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14. ABSTRACT This Toxicology Assessment was conducted in accordance with ASTM Guideline E-2552. Compounds evaluated are part of an effort to develop non-isocyanate-based polyurethane coatings for protection of erosion-prone components of military equipment and aircraft, such as helicopter rotor blades. Eight perfluorinated compounds were evaluated. In most cases, experimental data were not available, so predictions were made using Quantitative Structure-Activity (QSAR) models. In common with other perfluorinated compounds, many of these compounds are predicted to be developmental or reproductive toxicants, and to be recalcitrant in the environment. Compounds structurally similar to bisphenol A are at least potential endocrine disruptors. The two most favorable compounds are 2-(difluoroiodomethyl)-2,3,3-trifluorooxirane and 2,2,3,3,4,4,5,5-octafluorohexane-1,6-diamine. In vitro experimental testing is recommended.		
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TOXICOLOGY ASSESSMENT FOR DEPARTMENT OF DEFENSE STRATEGIC ENVIRONMENTAL RESEARCH AND DEVELOPMENT (SERDP) PROJECT WP-2601: SUSTAINABLE ENVIRONMENTALLY GREEN POLYURETHANES FOR EROSION-RESISTANT COATINGS MARCH 2016–JUNE 2018

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. Safeguarding the health of Service members, 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. This Toxicology Assessment has been prepared as part of this early evaluation of health and environmental hazards associated with new items of military materiel. Evaluations were conducted according to ASTM Guide E2552, *Assessing the Environmental and Human Health Impact of New Compounds for Military Use* and the U.S. Army Research, Development and Engineering Command Development Environmental Safety and Health Evaluation contribute to these overall objectives.

1.2 Purpose

This Toxicology Assessment was conducted for evaluating the toxicity of compounds proposed as components of a proposed replacement method for the preparation of polyurethane coatings. Polyurethane coatings are currently prepared using isocyanates and diisocyanate compounds that pose hazards to the health of workers involved in their preparation and application, and environmental hazards associated with waste disposal.

1.3 Conclusions

Because many of the compounds being considered are poorly represented in the QSAR training sets, confidence in the modeling predictions is lower than desirable; however, some indication of toxicity and physical behavior can be deduced from the predictions. Most of the compounds under consideration have low oral and inhalation toxicity and do not pose an unusual hazard from occupational exposure to skin and eyes. Many of the compounds under consideration are predicted to be possible developmental or reproductive toxicants by the TOPKAT program. Compounds that are structurally similar to bisphenol A (i.e., BPAF and PFBFP) are at least potential endocrine disruptors due to their predicted interactions with endocrine receptors. Genotoxicity predictions are generally favorable; carcinogenicity predictions are generally indeterminate, which is not uncommon with the TOPKAT program. Many of these fluorinated

organics have the strong potential to be environmentally persistent and bioaccumulate in biological systems if released to the environment from manufacturing.

Acute aquatic toxicity is predicted to be low for FIFO, Dioxolan, DAOFH, OFHDA, and DOHBC. Most compounds under consideration have limited solubility in aqueous systems, reducing the hazard to transport in groundwater, surface, and drinking water and toxicity toward aquatic species. However, all compounds under consideration with the exception of FIFO and OFHDA are predicted to be recalcitrant in the environment, which is a concern. FIFO and OFHDA are slowly biodegraded in the environment. Due to their limited volatility, UV-generated hydroxyl radicals will not degrade most of these compounds in the atmosphere.

Higher order polymers of these monomers are not expected to exhibit toxicity to either humans or environmental receptors due to lack of bioavailability, and hence exposure. Bioaccumulation by aquatic species is likewise not expected to be significant; however, persistence in the environment is likely significant due to lack of solubility and biodegradability.

1.4 Recommendations

Candidates selected for further development should receive a minimum battery of *in vitro* testing, to include the Ames mutagenicity test, an aquatic toxicity test (Microtox) and skin sensitization testing. Laboratory testing for biodegradability and soil leachability is also highly desirable.

2 REFERENCES

See Appendix A for list of references

3 AUTHORITY

Funding for this work was provided under Military Interdepartmental Purchase Request No. W74RDV70815535 dated 22 Mar 2017. This Toxicology Assessment addresses, in part, the following environment, safety, and occupational health (ESOH) requirements:

- Army Regulation (AR) 200-1, Environmental Protection and Enhancement, 2007;
- AR 40–5, Preventive Medicine, 2007;
- AR 70–1, Army Acquisition Policy, 2018;
- Department of Defense Directive 4715.1E, ESOH, 2005; Change 1, 2018; and
- Army Environmental Requirement and Technology Assessment Requirement PP-3-02-05, Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces, 2012.

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

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 PROBLEM

Polyurethane coatings are used in the Department of the Navy to provide erosion protection for military aircraft and shipboard surfaces such as helicopter blade leading edges, radomes, antennas and gun shields. The applicable standard is SAE AMD-C-83231. The standard synthetic pathway to polyurethane coatings has involved use of isocyanate and diisocyanate monomers as the starting materials. The diisocyanate compounds are known to be toxic to humans and the environment, and isocyanates may be prohibited from use in the near future as part of the prohibited and controlled chemical list. In addition, these specialty polyurethanes use high levels of volatile organic compounds (VOCs) and compounds designated as hazardous air pollutants. Currently, there are no environmentally-friendly wear-resistant coating alternatives capable of meeting the performance specification exist. The objective of this project is to develop a novel method for producing polyurethanes based upon non-isocyanate chemistries. The resulting polymeric non-isocyanate polyurethanes are expected to be sustainable, non- toxic, water-dispersible and/or dissolve in VOC-exempt solvents, and capable of being applied by conventional application methods.

6 METHODS

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

The properties necessary to assess fate and transport in the environment include—

- Molecular weight (MW).
- Boiling point (bp).
- Octanol-water partition coefficient (log K_{OW}).
- Organic carbon partition coefficient (log K_{OC}).
- Water solubility.
- Henry's law constant (K_H).
- Vapor pressure (vp).

Basic physical and chemical properties are usually determined by consulting tertiary sources when such information is available.

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity, and carcinogenicity; and mode(s) and mechanisms of toxicity. Toxicological information is derived directly from primary sources whenever possible.

Sources consulted in this search included *The Merck Index* (O'Neil 2006, Budavari 1996); the U.S. National Library of Medicine's Toxicology Data Network (TOXNET®) providing access to information from the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (USEPA); the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry; the USEPA ECOTOXicology Database System (ECOTOX); and the Defense Technical Information Center (DTIC®). Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health, the World Health Organization, the National Center for Biotechnology Information (NCBI) and the International Agency for Research on Cancer.

Table 1. Formulation Components

Chemical Substance	CAS Number
2-(Difluoroiodomethyl)-2,3,3-trifluorooxirane [FIFO]	Unknown
4,4'-(Perfluoropropane-2,2-diyl)bis(2-fluorophenol) [PFBFP]	Unknown
4,4'-(Perfluoropropane-2,2-diyl)phenol [BPAF]	1478-61-1
5,5'-((((Perfluoropropane-2,2-diyl)bis(2-fluoro-4,1-phenylene))bis(oxy)) bis(difluorometheylene))bis(4,4,5-trifluoro-1,3-dioxolan-2-one) [Dioxolan]	Unknown
2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diyl bis(4-methylbenzenesulfonate) [OFMBS]	Unknown
1,6-Diazido-2,2,3,3,4,4,5,5-octafluorohexane [DAOFH]	Unknown

Chemical Substance	CAS Number
2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diamine [OFHDA]	355-73-7
Diethyl (2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(carbonate) [DOHBC]	Unknown

Primary references are identified and retrieved using PubMed® and the ProQuest© Databases. TOXNET provides links to a suite of individual databases including ChemIDPlus® (chemical structures, registration numbers, and links to other sites providing physical chemical properties of the compound), the Hazardous Substances Data Bank (HSDB®), TOXLINE (references to literature on biochemical, pharmacological, physiological and toxicological effects of drugs and other chemicals), the Developmental and Reproductive Toxicology database, the Comparative Toxicogenomics Database, the Integrated Risk Information System, and the Animal Testing Alternatives database, as well as several others, including the archived databases for the Chemical Carcinogenesis Research Information System, the Carcinogenic Potency Database, and GENE-TOX genetic toxicity database. Commercial suppliers may provide results of in-house research that do not appear in the open literature.

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

7 RESULTS

7.1 Physical Properties

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

7.2 Compound Summaries

Table 4 contains summaries of mammalian toxicity data. Tables 5 and 6, respectively present assessments of human health and environmental toxicity for each of the formula components. Table 2 generalizes the criteria for each characterization. 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.

The potential for developmental or reproductive toxicity and genotoxicity derived from TOPKAT modeling in Table 4 is characterized according to the following scheme:

- Positive—Positive prediction at high confidence.
- Probable—Positive prediction at moderate confidence.
- Possible—Positive prediction at low confidence.
- Unlikely—Negative prediction at moderate confidence.
- Negative—Negative prediction at high confidence.

Table 2. Categorization Criteria used in the Development of Environmental Safety and Occupational Health Severity (modified from Howe et al. 2006)

	Low	Moderate	High
PERSISTENCE	Readily biodegrades (<28 days)	Degradation ½ life: water <40 days , soil <120 days	Degradation ½ life: water >40 days soil > 120 days
TRANSPORT	Water sol. < 10 mg/L log K_{OC} > 2.0	Water sol. 10-1000 mg/L log K_{OC} 2.0-1.0	Water sol. > 1000 mg/L log Koc <1.0
BIOACCUMULATION	log K_{OW} <3.0	log K_{OW} 3.0-4.5	log K_{OW} >4.5
TOXICITY	No evidence of carcinogenicity/ mutagenicity; Subchronic LOAEL > 200 mg/kg-day	Mixed evidence for carcinogenicity/mutagenicity (B2, 2); Subchronic LOAEL 5-200 mg/kg-day	Positive corroborative evidence for carcinogenicity/ mutagenicity; LOAEL < 5 mg/kg-day
ECOTOXICITY	Acute LC_{50}/LD_{50} >1 mg/L or 1500 mg/kg; Subchronic EC_{50} >100 µg/L or LOAEL >100 mg/kg-day	Acute LC_{50}/LD_{50} 1-0.1 mg/L or 1500-150 mg/kg; Subchronic EC_{50} 100-10 µg/L or LOAEL – 10-100 mg/kg-day	Acute LC_{50}/LD_{50}<100 µg/L or <150 mg/kg; Subchronic LOAEL <10 mg/kg-day

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

Table 3. Physical Properties

Compound	Molar Mass (g/mol)	Melting Point (ºC)	Boiling Point (ºC)	Aqueous solubility (mg/L) @ 25ºC	log K_{OW}	log K_{OC}	Henry's Law Constant (atm-m^3/mol) @ 25ºC	Vapor Pressure mmHg @ 25°C
FIFO	273.93[a]	-25.78[a]	103.08[a]	117.9[a]	2.54[a]	2.24[a]	3.71E-04[a]	38[a]
PFBFP	372.22[a]	128.48[a]	341.72[a]	1.185[a]	4.88[a]	3.96[a]	7.74E-10[a]	1.7E-06[a]
BPAF	336.24[b]	161-163[b]	400[c]	4.30[a]	2.818[b] 4.47[a] 5.5[c]	7.6E+05[a]	5.7E-10[a]	5.4E-07[a]
Dioxolan	680.31[a]	292.2[a]	670.52[a]	4.81E-06[a]	8.19[a]	5.11[a]	1.10E-06[a]	1.09E-15[a]
OFMBS	570.47[a]	219.46[a]	514.69[a]	0.00248[a]	5.86[a]	4.49[a]	1.09E-08[a]	9.75E-11[a]
DAOFH	312.13[a]	245.92[a]	571.3[a]	0.0146[a]	6.35[a]	5.30[a]	4.33E-04[a]	1.65E-12[a]
OFHDA	260.06[d]	16.16[a]	138.45[a]	8215[a]	2.85[e]	1.79[a]	7.89E-07[a]	6.82[a]
DOHBC	406.38[a]	39.70[a]	322.26[a]	0.511[a]	4.38[a]	2.89[a]	9.32E-03[a]	4.37E-04[a]

Notes:
[a] EPI Suite prediction (USEPA 2017)
[b] Sigma 2014
[c] National Toxicology Program (NTP 2008)
[d] PubChem 2018b
[e] ChemSrc 2018

Table 4. Toxicity Data

Compound	Acute Oral LD_{50} (mg/kg)	Chronic Oral LOAEL (mg/kg-d)	Inhalation LC_{50} (g/m^3-h)	Dermal	Ocular	Development/ Reproduction	Genotoxicity	Carcinogenicity
FIFO	>10,000[a]	1.1[a]	>10[a]	Possible irritant; sensitizer[a]	Probable mild irritant[a]	Negative[a]	Probable[a]	Indeterminate[a]
PFBFP	0.747[a]	22.3[a]	>10[a]	Unlikely irritant or sensitizer[a]	Probable irritant[a]	Possible[a]	Unlikely[a]	Indeterminate[a]
BPAF	3400[b]	31.1[a]	>10[a]	Irritant[c]; possible sensitizer[a]	Irritant[a]	Possible[a]	Negative[a]	Negative[a]
Dioxolan	0.180[a]	3.3[s]	ND	Possible irritant; severe sensitizer[a]	Possible irritant[a]	Possible[a]	Unlikely[a]	ND
OFMBS	76.6[a]	26.5[A]	4.47E-04[a]	Unlikely irritant; probable sensitizer[a]	Probable severe irritant[a]	Possible[a]	Probable[a]	Indeterminate[a]
DAOFH	475.4[a]	112.6[A]	>10[a]	Probable irritant; unlikely sensitizer[a]	Unlikely irritant[a]	Possible[a]	Probable[a]	Indeterminate[a]
OFHDA	366.6[a]	82.7[A]	>10[a]	Probable irritant; unlikely sensitizer[a]	Possible severe irritant[a]	Unlikely[a]	Negative[a]	Indeterminate[a]
DOHBC	1600[a]	22.3[A]	>10[a]	Probable irritant; unlikely sensitizer[a]	Indeterminate[a]	Positive[a]	Negative[a]	Possible[a]

Legend:
ND = No data
Notes:
[a] TOPKAT model estimate (BIOVIA 2015)
[b] PubChem 2018b
[c] Sigma 2014

Table 5. Toxicity Assessment

Compound	Oral	Inhalation	Dermal	Ocular	Carcinogenicity	Comments
FIFO	Low	Low	Mod	Mod	Unk	Not expected to be a developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
PFBFP	High	Low	Low	Mod	Unk	Possible developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
BPAF	Mod	Low	Mod	Mod	Low	Probable endocrine disruptor; Possible developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
Dioxolan	High	Unk	Mod	Mod	Low	Possible developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
OFMBS	High	High	Mod	Mod	Unk	Possible developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
DAOFH	Mod	Low	Mod	Mod	Unk	Possible developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.

OFHDA	Mod	Low	Mod	Mod	Unk	Not predicted to be a developmental/ reproductive toxicant. The bioaccumulation potential of this halongenated organic may be significant.
DOHBC	Mod	Low	Mod	Unk	Mod	Probable developmental/ reproductive toxicant.

Table 6. Ecotoxicity Assessment

Compound	Aquatic	Terrestrial Invertebrates	Terrestrial Plants	Mammals	Birds	Comments
FIFO	Low	Unk	Unk	Low	Unk	Not readily biodegradable
PFBFP	High	Unk	Unk	High	Unk	Recalcitrant
BPAF	Mod	Unk	Unk	Mod	Unk	Recalcitrant
Dioxolan	Low	Unk	Unk	High	Unk	Recalcitrant
OFMBS	High	Unk	Unk	High	Unk	Recalcitrant
DAOFH	Low	Unk	Unk	Mod	Unk	Recalcitrant
OFHDA	Low	Unk	Unk	Mod	Unk	Not readily biodegradable
DOHBC	Low	Mod	Unk	Mod	Unk	Recalcitrant

7.3 2-(Difluoroiodomethyl)-2,3,3-trifluorooxirane [FIFO]

7.3.1 General Information

FIFO is predicted to be a liquid under typical ambient conditions.

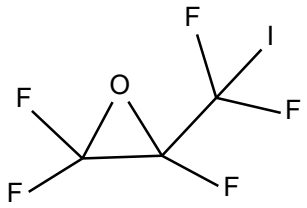

Figure 1. 2-(Difluoroiodomethyl)-2,3,3-trifluorooxirane

7.3.2 Toxicology Data

No experimental data were found. All information below is based upon QSAR modeling. Given the halogenated nature of this organic molecule, bioaccumulation and environmental persistence may be a concern.

7.3.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of more than 10,000 mg/kg at high confidence. The LOAEL is predicted to be 1.1 milligrams per kilogram per day (mg/kg-day), also at high confidence. The inconsistency between these two values is unusually large, but it is not possible to assign which has the higher accuracy. Based on the estimated LD_{50}, this corresponds to a classification of low for acute toxicity in the APHC system, and unclassified in the GHS system.

7.3.2.2 Inhalation

The TOPKAT modeling predicts an inhalation LC_{50} of more than 10 grams per cubic meter per hour (g/m^3-hour) at high confidence. This corresponds to a classification of low inhalation toxicity in the APHC system and unclassified in the GHS system.

7.3.2.3 Dermal

The TOPKAT modeling predicts FIFO is possibly a dermal irritant and sensitizer, but at low confidence.

7.3.2.4 Ocular

The TOPKAT modeling predicts FIFO is likely a mild ocular irritant.

7.3.2.5 Development and Reproduction

The TOPKAT modeling predicts FIFO will not be a developmental or reproductive toxicant at high confidence.

7.3.2.6 Neurotoxicity

No information on neurotoxicity is currently available.

7.3.2.7 Genotoxicity

The TOPKAT modeling predicts FIFO will be mutagenic in the Ames assay at moderate confidence.

7.3.2.8 Carcinogenicity

The TOPKAT modeling of carcinogenicity for FIFO is indeterminate.

7.3.2.9 Ecotoxicology

7.3.2.9.1 Fate and Transport

The FIFO is predicted to be slightly soluble with only a moderate ability to bind to organic carbon, making it a low to moderate hazard for transport in groundwater, and posing a moderate hazard to surface and drinking water. The FIFO is expected to be slightly volatile from water or wet surfaces based on its predicted Henry's Law constant, but will evaporate readily from dry surfaces. The FIFO is expected to exist in the atmosphere primarily as a vapor. The USEPA's EPI Suites program (USEPA 2017) was unable to predict an air oxidation half-time, but persistence in the environment is expected to be weeks to months. The FIFO is not expected to bioconcentrate in aquatic organisms.

7.3.2.9.2 Ecotoxicity

No experimental data were available. The USEPA ECOSAR 2.0 program (USEPA 2018) models FIFO as a haloepoxide. The 96-hour EC_{50} in green algae is predicted to be 5.050 mg/L, the 48-hour LC_{50} in *Daphnia* to be 4.968 mg/L, and the 96-hour LC_{50} in fish 9.721 mg/L, all indicating low toxicity toward aquatic species.

7.3.2.9.3 Degradation/Treatment

The EPI Suites (USEPA 2017) predicts FIFO will not be readily biodegradable, with environmental persistence from weeks to months. The FIFO is predicted to be removed to a limited extent (17%) by physical wastewater treatment processes, primarily by evaporation to the atmosphere.

7.4 4,4'-(Perfluoropropane-2,2-diyl)bis(2-fluorophenol) [PFBFP]

7.4.1 General Information

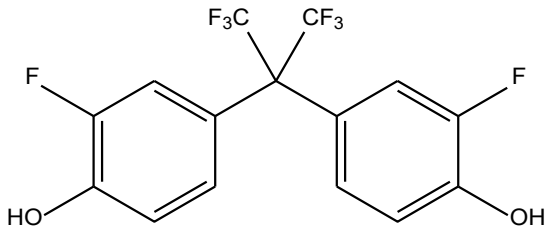

Figure 2. 4,4'-(Perfluoropropane-2,2-diyl)bis(2-fluorophenol)

7.4.2 Toxicology Data

No experimental data were found. All information below is based upon QSAR modeling. Given the halogenated nature of this organic molecule, bioaccumulation and environmental persistence may be a concern.

7.4.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of 0.747 mg/kg at low confidence; the chronic LOAEL is predicted to be 22.3 mg/kg-day at low confidence. The LOAEL value is considered to be invalid since it is greater than the LD_{50}. This corresponds to a classification of high for acute toxicity in the APHC system and the GHS system, but this prediction is of low confidence and is inconsistent with the predicted inhalation toxicity, which is of high confidence.

7.4.2.2 Inhalation

The TOPKAT modeling predicts the acute inhalation LC_{50} in rats to be greater than 10 g/m^3-hour at high confidence. This corresponds to a classification of low inhalation toxicity in the APHC system and unclassified in the GHS system.

7.4.2.3 Dermal

The TOPKAT modeling predicts PFBFP is an unlikely dermal irritant or sensitizer, but at low confidence.

7.4.2.4 Ocular

The TOPKAT modeling predicts PFBFP is a probable ocular irritant.

7.4.2.5 Development and Reproduction

The TOPKAT modeling predicts PFBFP will be a developmental or reproductive toxicant, but at low confidence.

7.4.2.6 Neurotoxicity

No data on neurotoxicity was found.

7.4.5.7 Genotoxicity

The TOPKAT modeling predicts PFBFP will not be mutagenic in the Ames assay, but at low confidence.

7.4.2.8 Carcinogenicity

The TOPKAT modeling of carcinogenicity for PFBFP is indeterminate.

7.4.2.9 Ecotoxicology

7.4.2.9.1 Fate and Transport

The PFBFP is predicted to be only slightly soluble with a high affinity for organic carbon, making it a low hazard for transport in groundwater, and an unlikely threat to surface or drinking water.
The PFBFP will not readily partition to the atmosphere from water or wet surfaces based on its predicted Henry's Law constant, and are not prone to evaporation from dry surfaces. The PFBFP will exist in the atmosphere as a vapor-particulate mix, and the air oxidation half-time is predicted to be 4.7 hours, but PFBFP is predicted to be recalcitrant in the environment. The PFBFP is predicted to have a high tendency for bioconcentration (USEPA 2017).

7.4.2.9.2 Ecotoxicity

No experimental data were available. The USEPA ECOSAR 2.0 program (USEPA 2018) models PFBFP as a polyphenol. The 96-hour EC_{50} in green algae is predicted to be 0.832 mg/L, the 48-hour LC_{50} in *Daphnia* is 0.965 mg/L, and the 96-hour LC_{50} in fish is 0.386 mg/L, all indicating high toxicity toward aquatic species and classification in GHS acute aquatic toxicity category I.

7.4.2.9.3 Degradation/Treatment

The EPI Suites (USEPA 2017) predicts PFBFP will not be biodegradable, but recalcitrant in the environment. The PFBFP will be readily removed (73.5%) from waste streams by physical wastewater treatment processes, primarily by sludge adsorption.

7.5 4,4'-(Perfluoropropane-2,2-diyl)phenol [BPAF]

7.5.1 General Information

4,4'-(Perfluoropropane-2,2-diyl)diphenol is also known as Bisphenol AF, and has been used as a substitute for bisphenol A in synthetic polymer materials. It is an off-white powder. It is used as a crosslinking agent for certain fluoroelastomers and as a monomer for polyimides, polyamides, polyesters, polycarbonate copolymers and other specialty polymers.

Synonyms include:

- 1,1,1,3,3,3-hexafluoro-2,2-bis(4-hydroxyphenyl)propane;
- 2,2-bis(4´-hydroxyphenyl) hexafluoropropane;
- 2,2-bis(4-hydroxyphenyl)-1,1,1,3,3,3-hexafluoropropane;
- 2,2-bis(4-hydroxyphenyl)hexafluoropropane;
- 2,2-bis(4-hydroxyphenyl)perfluoropropane;
- 2,2-bis(*p*-hydroxyphenyl)hexafluoropropane;
- 4,4´-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bisphenol;
- 4,4´-(hexafluoroisopropylidene)diphenol;
- 4,4´-[trifluoro-1-(trifluoromethyl)ethylidene]diphenol;
- hexafluorobisphenol A;
- hexafluorodiphenylolpropane;
- hexafluoroisopropylidenebis(4-hydroxybenzene);
- 4,4´-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis-phenol;
- 4,4´-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]di-phenol; and
- 4,4´-[trifluoro-1-(trifluoromethyl)ethylidene]di-phenol (NTP 2008).

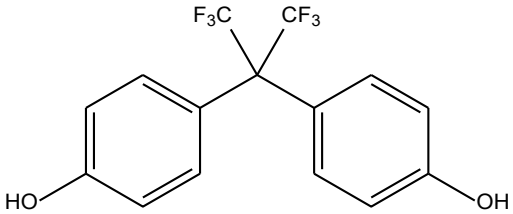

Figure 3. 4,4'-(Perfluoropropane-2,2-diyl)phenol

7.5.2 Toxicology Data

7.5.2.1 Oral

The oral LD_{50} in rats is reported to be 3,400 mg/kg, with unspecified effects on the gastrointestinal system, liver, kidney, ureter, and bladder (Sigma 2014). Classification of acute oral toxicity is low in the APHC system, and is unclassifiable in the GHS.

No experimental chronic toxicity data were found. The TOPKAT modeling predicts a chronic LOAEL in rats of 31.3 mg/kg-day at low confidence.

7.5.2.2 Inhalation

The TOPKAT modeling predicts an LC_{50} in rats of >10 g/m^3-hour at high confidence.

According to a supplier SDS, BPAF is classified in GHS category 3 for specific organ toxicity-single exposure, indicating it may cause respiratory irritation (Sigma 2014).

7.5.2.3 Dermal

According to a supplier SDS, BPAF is classified as a category 2–skin irritant in the GHS system (Sigma 2014).

The TOPKAT modeling predicts BPAF may be a skin sensitizer.

7.5.2.4 Ocular

According to a supplier SDS, BPAF is classified as a category 2A ocular irritant in the GHS system (Sigma 2014).

7.5.2.5 Development and Reproduction

The Feng et al. (2012) exposed male Sprague-Dawley rats to 0, 2, 10, 50, or 200 mg BPAF/kg-day for a period of 14 days. Total cholesterol levels in serum were decreased in rats given a dose of 50 or 200 mg/kg-day. The BPAF concentration in the testes increased with increasing dose of BPAF. Reduced serum testosterone and increased luteinizing hormone (LH) and follicle-stimulating hormone levels were observed in the higher dose groups. The BPAF exposure also resulted in a dramatic decline in genes and proteins involved in cholesterol biosynthesis, transport, and steroid biosynthesis. Testicular mRNA levels of inhibin B, estrogen receptor α, and LH receptor also decreased in rats given a dose of 200 mg/kg-day. BPAF appears to interfere with the testosterone biosynthesis pathway.

The BPAF was compared to bisphenol A in its ability to bind to estrogen receptors (ER) α and β and the bisphenol A-speciifc estrogen related receptor ERRγ. The BPAF was found to bind more strongly to the estrogen receptors than the ERRγ. The BPAF receptor-binding activity was three times stronger for ERβ than for ERα. The BPAF was a full agonist for ERα, but was almost completely inactive in stimulating the basal constitutive activity of ERβ (Matsushima et al. 2010).

The Delfosse et al. (2012) compared the mechanism by which bisphenols A, AF, and C bind to ER α and β with that used by 17β-estradiol. The bisphenols were found to be partial agonists of ERs by activating the N-terminal activation function 1 regardless of their effect on the C-terminal activation function 2, which ranges from weak agonism (with BPA) to antagonism (with BPC). Crystallographic analysis of the interaction between bisphenols and ERs reveals two discrete binding modes, reflecting the different activities of compounds on ERs. The BPA and 17β-estradiol bind to ERs in a similar fashion, whereas, with a phenol ring pointing toward the activation helix

H12, the orientation of BPC accounts for the marked antagonist character of this compound. Based on structural data, a protocol was developed for *in silico* evaluation of the interaction between bisphenols and ERs or other members of the nuclear hormone receptor family.

Developmental toxicity was assessed via the uterotrophic assay where both male and female rats were injected subcutaneously with 8, 40, or 100 mg/kg-day for 3 days. No clinical abnormalities were noted. Body weight increases were normal. Uterine water content was grossly detected at 100 mg/kg-day; uterine blotted weight increased at all doses (Yamasaki et al. 2003a, 2003b).

7.5.2.6 Neurotoxicity

Lee et al. (2013) investigated the neurotoxicity of BPAF on the hippocampal cell line HT-22. BPAF induced apoptosis in both HT-22 and primary neuronal cells. The BPAF was found to increase the level of intracellular calcium, followed by the generation of reactive oxygen species (ROS). The BPAF upregulated the phosphorylation of mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase, p38 and c-Jun N-terminal kinase (JNK), and nuclear translocation of nuclear factor-κB. The BPAF also inhibited microglial activation in a microglia/neuroblastoma co-culture model by the reduction of nitric oxide production. The BPAF disrupted the normal physiologic functions of microglia at non-toxic levels.

7.5.6.7 Genotoxicity

According to a supplier SDS, BPAF has been tested in hamster and lung cells, and the micronucleus test (Sigma 2014).

The Kanai et al. (2001) compared the cell-transforming activity of bisphenol A (BPA), its analogs, and their estrogenicity. The BPAF was referred to as BPA-5 in this report. Transforming activity was determined in Syrian hamster embryo cells lacking estrogen-receptor expression. Although it was not the most potent analog tested, BPAF was found to have more transforming activity than BPA. The study also compared the estrogenicity of the tested compounds in MCF7 human breast cancer cells as determined by cell proliferation or progesterone receptor expression. In this test, BPAF was the closest to BPA in activity, although somewhat less. The study concluded that the transforming activity of bisphenol compounds did not correlate with their ability to interact with estrogen receptors.

The Pfeiffer et al. (1997) studied BPA and four analogs for their aneuploidic potential by determining ability to interfere with microtubule formation in Chinese hamster V79 cells and the ability to create micronuclei. At concentrations without gross cytotoxicity, BPA and all fluoro-alkylated and ring-methylated analogs were active at all endpoints tested. This result indicates BPAF has the potential to induce aneuploidy.

7.5.2.8 Carcinogenicity

BPAF is not considered to be carcinogenic (Sigma 2014).

7.5.2.9 Ecotoxicology

7.5.2.9.1 Fate and Transport

If released to soil, BPAF is expected to not be mobile based upon an estimated Koc of $7.6x10^5$. The estimated pKa of bisphenol AF is 9.2. This indicates that this compound will be primarily protonated at near neutral pH and is expected to bind more strongly to soils with high organic content. If soil pH increases, the compound will exist partially in anionic form and anions generally do not adsorb as strongly to soils their neutral counterparts, especially in soils with higher clay content. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of $5.7X10^{-10}$ atm-m^3/mole. The BPAF is not expected to volatilize from dry soil surfaces based upon its vapor pressure. Biodegradation data in soil or water were not available. If released into water, bisphenol AF is expected to adsorb to suspended solids and sediment based upon the estimated Koc. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated bioconcentration factor (BCF) of 420 suggests the potential for bioconcentration in aquatic organisms is high (PubChem 2018).

If released to air, an estimated vapor pressure of $5.4x10^{-7}$ mm Hg at 25 ºC indicates BPAF will exist in both the vapor and particulate phases in the atmosphere. Particulate-phased bisphenol AF will be removed from the atmosphere by wet and dry deposition (PubChem 2018).

7.5.2.9.2 Ecotoxicity

Experimental testing in Japanese medaka (*Oryzias latipes*) found induction of genetic changes at concentrations as low as 0.5 µM (ECOTOX 2018).

The USEPA's ECOSAR program models BPAF as a polyphenol. The 96-hour EC_{50} in green algae is predicted to be 1.026 mg/L, the 48-hour LC_{50} in *Daphnia* is predicted to be 1.772 mg/L, and the 96-hour LC_{50} in fish is predicted to be 0.605 mg/L. These predictions would place BPAF in GHS acute aquatic toxicity Category I.

7.5.2.9.3 Degradation/Treatment

The BPAF is predicted to not be biodegradable in the environment, and is expected to be recalcitrant except when degraded by photochemically-produced hydroxyl radicals. Vapor-phase BPAF will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 1.6 hours.

The BPAF is predicted to be effectively removed (54.4%) by physical wastewater treatment plant processes, almost exclusively by sludge adsorption.

7.6 5,5'-((((perfluoropropane-2,2-diyl)bis(4,1-phenylene))bis(oxy)bis(difluoromethylene))bis(4,4-difluoro-1,3-dioxolan-2-one) [Dioxolan]

7.6.1 General Information

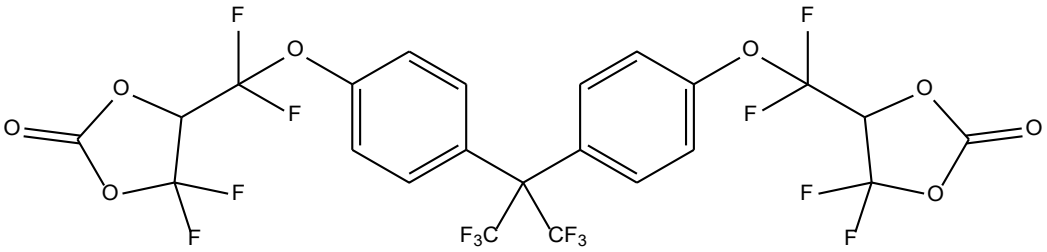

Figure 4. 5,5'-((((Perfluoropropane-2,2-diyl)bis(4,1-phenylene))bis(oxy))bis(difluoromethylene))bis(4,4-difluoro-1,3-dioxolan-2-one)

7.6.2 Toxicology Data

Experimental data on dioxolan could not be found. All information below is based upon QSAR predictions; however, confidence in these predictions is low due to lack of sufficient coverage in the training sets. Given the halogenated nature of this organic molecule, bioaccumulation and environmental persistence may be a concern.

7.6.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of 0.180 mg/kg at low confidence. The chronic LOAEL is predicted to be 3.3 mg/kg-day, also at low confidence. If borne out, these predictions would classify dioxolan as having high toxicity in both the APHC and GHS (Category 1).

7.6.2.2 Inhalation

The TOPKAT was unable to predict a value for inhalation toxicity.

7.6.2.3 Dermal

The TOPKAT modeling predicts dioxolan is a possible dermal irritant and severe sensitizer.

7.6.2.4 Ocular

The TOPKAT modeling predicts dioxolan is possibly an irritant.

7.6.2.5 Development and Reproduction

The TOPKAT modeling predicts dioxolan will be a developmental or reproductive toxicant, but at low confidence.

7.6.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.6.2.7 Genotoxicity

The TOPKAT modeling predicts dioxolan will not be mutagenic in the Ames test, at low confidence.

7.6.2.8 Carcinogenicity

The TOPKAT modeling of carcinogenicity for dioxolan is unreliable.

7.6.2.9 Ecotoxicology

7.6.2.9.1 Fate and Transport

If released to soil or water, dioxolan is not anticipated to be a groundwater transport hazard due to low solubility and high affinity for organic carbon. Partition to the atmosphere is expected to be almost non-existent based upon the value of the Henry's Law constant. Partition to the atmosphere from dry surfaces is also not a significant fate process, and any dioxolan in the atmosphere is expected to exist as a particulate. The BCF is calculated to be 3,478 liters per kilogram-wet weight, but bioaccumulation is expected to be limited by the insolubility of dioxolan.

7.6.2.9.2 Ecotoxicity

No experimental data were found. The USEPA's ECOSAR program models dioxolan as an ester. The 96-hour EC_{50} in green algae is predicted to be 0.004 mg/L, the 48-hour LC_{50} in *Daphnia* is
0.024 mg/L, and the 96-hour LC_{50} in fish is 0.022 mg/L. Each of these values is greater than the predicted solubility limit of dioxolan, so there should be no toxicity at saturation.

7.6.2.9.3 Degradation/Treatment

Dioxolan is predicted to not be biodegradable and is recalcitrant in the environment.

Removal of dioxolan from waste streams by physical wastewater treatment is predicted to be high (94%) because of high affinity to treatment plant sludge.

7.7 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diyl bis(4-methylbenzenesulfonate) [OFMBS]

7.7.1 General Information

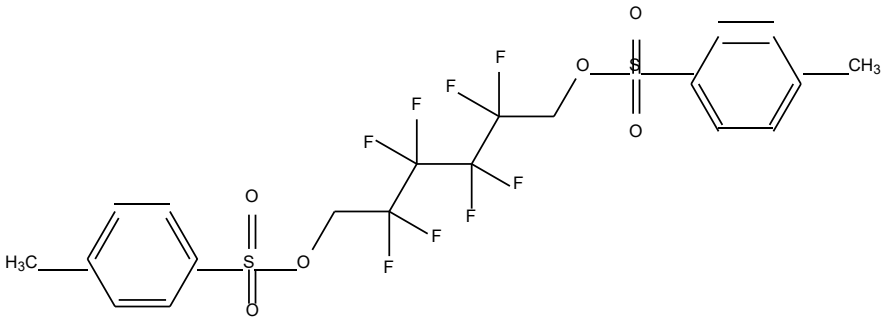

Figure 5. 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diyl bis(4-methylbenzenesulfonate)

7.7.2 Toxicology Data

7.7.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of 76.6 mg/kg at low confidence. The chronic LOAEL is predicted to be 26.5 mg/kg-day at moderate confidence. These values would categorize OFMBS as high toxicity under APHC criteria and Category 3 in the GHS. Given the halogenated nature of this organic molecule, bioaccumulation and environmental persistence may be a concern.

7.7.2.2 Inhalation

The TOPKAT modeling is unable to predict a median LC_{50} in rats, but projects an upper limit of toxicity as 0.447 milligrams per cubic meter per hour (mg/m^3-hour) at low confidence. This value would categorize OFMBS as highly toxic under APHC criteria and Category 1 in the GHS.

7.7.2.3 Dermal

The TOPKAT modeling predicts OFMBS is not likely to be an irritant, but is probably a dermal sensitizer.

7.7.2.4 Ocular

The TOPKAT modeling predicts OFMBS will be a severe ocular irritant.

7.7.2.5 Development and Reproduction

The TOPKAT modeling predicts OFMBS will be a developmental or reproductive toxicant, but at low confidence.

7.7.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.7.2.7 Genotoxicity

The TOPKAT modeling predicts OFMBS will be positive in the Ames mutagenicity test, but at low confidence.

7.7.2.8 Carcinogenicity

The TOPKAT modeling of OFMBS for carcinogenicity is indeterminate.

7.7.2.9 Ecotoxicology

7.7.2.9.1 Fate and Transport

The OFMBS is unlikely to be mobile in soil or groundwater due to insolubility and high affinity for organic carbon. Partition to the atmosphere from water or wet surfaces is not expected to occur due to the high Henry's Law constant; evaporation from dry surfaces is also unlikely due to the very low vapor pressure. Any OFMBS found in the atmosphere will be present as a particulate. Bioaccumulation is a possibility due to the very high log Kow (and halogenation of the organic molecule), but may be limited by low solubility. The bioaccumulation potential may also be of human relevance.

7.7.2.9.2 Ecotoxicity

The USEPA's ECOSAR program models OFMBS as an ester. The ECOSAR predicts a 96-hour EC_{50} in green algae of 0.135 mg/L. Acute values for fish and *Daphnia* could not be calculated because the log Kow exceeded the parameters of the program. However, chronic values were computed to be 0.121 mg/L for green algae, 0.131 mg/L for *Daphnia*, and 0.014 mg/L for fish, all of which are greater than the predicted solubility of OFMBS.

7.7.2.9.3 Degradation/Treatment

The OFMBS is not expected to be biodegradable and will be recalcitrant in the environment. Removal by physical wastewater treatment processes will be high (91.4%) primarily by sludge adsorption.

7.8 1,6-Diazido-2,2,3,3,4,4,5,5-octafluorohexane [DAOFH]

7.8.1 General Information

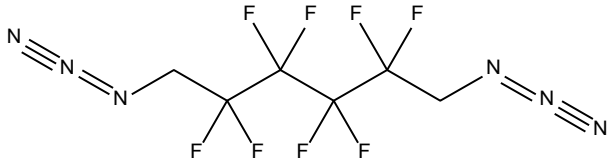

Figure 6. 1,6-Diazido-2,2,3,3,4,4,5,5-octafluorohexane

7.8.2 Toxicology Data

Experimental data on DAOFH could not be found. All information below is based upon QSAR predictions; however, confidence in these predictions is often low due to lack of sufficient coverage in the training sets. The bioaccumulation potential of this molecule due to the addition of the fluorine moieties may be of human and environmental relevance.

7.8.2.1 Oral

The TOPKAT modeling predicts and acute oral LD_{50} in rats of 475.4 mg/kg at low confidence. The chronic LOAEL is predicted to be 112.6 mg/kg-day at high confidence. These values would make DAOFH moderately toxic under the APHC system, and Category 4 in the GHS.

7.8.2.2 Inhalation

The TOPKAT modeling predicts an inhalation LC_{50} in rats greater than 10 g/m^3-hour at moderate confidence.

7.8.2.3 Dermal

The TOPKAT modeling predicts DAOFH is probably a skin irritant, but an unlikely sensitizer.

7.8.2.4 Ocular

The TOPKAT modeling predicts DAOFH is an unlikely ocular irritant.

7.8.2.5 Development and Reproduction

The TOPKAT modeling predicts DAOFH will be a developmental or reproductive toxicant at low confidence.

7.8.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.8.2.7 Genotoxicity

The TOPKAT modeling predicts DAOFH will test positive in the Ames mutagenicity test at low confidence.

7.8.2.8 Carcinogenicity

The TOPKAT modeling of carcinogenicity for DAOFH is indeterminate.

7.8.2.9 Ecotoxicology

7.8.2.9.1 Fate and Transport

If released to soil or groundwater, DAOFH is not expected to be a groundwater transport hazard due to low solubility and high affinity for organic carbon. Partition to the atmosphere from water or wet surfaces is expected to be moderate, but any DAOFH in the atmosphere is expected to be in particulate form. Partition to the atmosphere from dry surfaces is not expected due to the extremely low vapor pressure. Bioconcentration in aquatic species is expected to be limited by compound solubility.

7.8.2.9.2 Ecotoxicity

No experimental data were found. The USEPA's ECOSAR program models DAOFH as a neutral organic. The 96-hour EC_{50} in green algae is predicted to be 0.106 mg/L, the 48-hour LC_{50} in *Daphnia* is 0.027 mg/L, and the 96-hour LC_{50} in fish is 0.032 mg/L. Each of these values is greater than the predicted solubility of DAOFH, so there should be no mortality at saturation.

7.8.2.9.3 Degradation/Treatment

The DAOFH is predicted to not be biodegradable and is recalcitrant in the environment.

Removal of DAOFH by wastewater treatment plants is predicted to be high (93.2%), almost exclusively by sludge adsorption.

7.9 2,2,3,3,3,4,4,5,5-Octafluorohexane-1,6-diamine [OFHDA]

7.9.1 General Information

Synonyms include:

- 2,2,3,3,4,4,5,5-Octafluoro-1,6-hexamethylenediamine;
- 1,6-Hexanediamine, 2,2,3,3,4,4,5,5-octafluoro;
- 2,2,3,3,4,4,5,5-octafluoro-hexanediyldiamine; and
- 2,2,3,3,4,4,5,5-Octafluor-hexandiyldiamin (ChemSrc 2018).

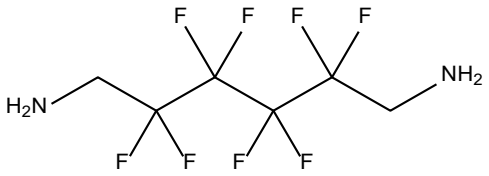

Figure 7. 2,2,3,3,3,4,4,5,5-Octafluorohexane-1,6-diamine

7.9.2 Toxicology Data

No experimental information was found. All information below is based upon QSAR modeling. The bioaccumulation potential may be of human and environmental relevance.

7.9.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of 366.6 mg/kg at low confidence. The LOAEL is predicted to be 82.7 mg/kg-day at high confidence. This corresponds to a classification of moderate for acute toxicity in the APHC system, and Category 4 in the GHS (OSHA 2012).

7.9.2.2 Inhalation

The TOPKAT modeling predicts an inhalation LC_{50} of more than 10 g/m^3-hour at high confidence. This corresponds to a classification of low inhalation toxicity in the APHC system and unclassified in the GHS system (Table 2) (OSHA 2012).

7.9.2.3 Dermal

The TOPKAT modeling predicts OFHDA is a probable dermal irritant, but an unlikely sensitizer.

7.9.2.4 Ocular

The TOPKAT modeling predicts OFHDA is possibly a severe ocular irritant.

7.9.2.5 Development and Reproduction

The TOPKAT modeling predicts OFHDA will not be a developmental or reproductive toxicant at low confidence.

7.9.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.9.2.7 Genotoxicity

The TOPKAT modeling predicts OFHDA will not be mutagenic in the Ames assay at low confidence.

7.9.2.8 Carcinogenicity

The TOPKAT modeling of carcinogenicity for OFHDA is indeterminate.

7.9.2.8 Ecotoxicology

7.9.2.8.1 Fate and Transport

If discharged to soil, OFHDA is expected to pose a moderate to high groundwater transport hazard due to relatively high solubility and low log Koc, and will probably pose a hazard to surface and drinking water. The OFHDA is considered slightly volatile from water or wet surfaces based upon the predicted Henry's Law constant, but should readily evaporate from dry surfaces. The OFHDA will exist in the atmosphere primarily as a vapor. The OFHDA is not expected to bioaccumulate in aquatic species.

7.9.2.8.2 Ecotoxicity

No experimental data were available. The USEPA ECOSAR 2.0 program (USEPA 2018) models OFHDA as an aliphatic amine. The 96-hour EC_{50} in green algae is predicted to be 8.66 mg/L, the 48-hour LC_{50} in *Daphnia* to be 9.68 mg/L, and the 96-hour LC_{50} in fish to be 84.59 mg/L; thus all indicating lack of toxicity toward aquatic species.

7.9.2.8.3 Degradation and Treatment

The OFHDA is predicted to not be readily biodegradable, and the air oxidation potential half-time is estimated at 634 days by EPI Suites. Persistence in the environment is predicted to be from weeks to months. The OFHDA is predicted to be poorly removed (~2%) by physical wastewater treatment processes, primarily by sludge adsorption.

7.10 Diethyl (2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(carbonate) [DOHBC]

7.10.1 General Information

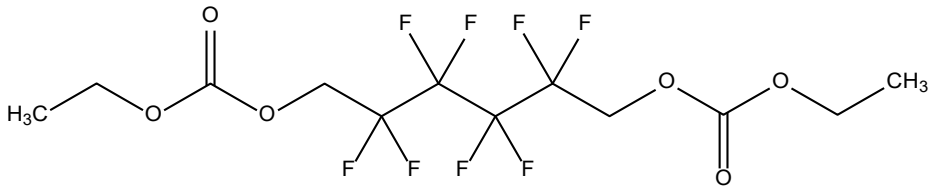

Figure 8. Diethyl (2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(carbonate)

7.10.2 Toxicology Data

7.10.2.1 Oral

The TOPKAT modeling predicts an acute oral LD_{50} in rats of 1,600 mg/kg at low confidence. The chronic LOAEL is predicted to be 22.3 mg/kg-day at high confidence. These values are consistent with moderate toxicity in the APHC system, and Category 4 in the GHS. The bioaccumulation potential of the halogenated organic may be significant.

7.10.2.2 Inhalation

The TOPKAT modeling predicts an LC_{50} in rats of >10 g/m^3-hour at high confidence. This would classify DOHBC as non-toxic in the APHC system and the GHS.

7.10.2.3 Dermal

The TOPKAT modeling predicts DOHBC is possibly a dermal irritant, but is probably not a sensitizer.

7.10.2.4 Ocular

The TOPKAT modeling for ocular effects is indeterminate.

7.10.2.5 Development and Reproduction

The TOPKAT modeling predicts DOHBC will be a developmental or reproductive toxicant at high confidence.

7.10.2.6 Neurotoxicity

No information on neurotoxicity was found.

7.10.2.7 Genotoxicity

The TOPKAT modeling predicts DOHBC will not be mutagenic in the Ames test at low confidence.

7.10.2.8 Carcinogenesis

The TOPKAT modeling predicts DOHBC is possibly carcinogenic.

7.10.2.9 Ecotoxicology

7.10.2.9.1 Fate and Transport

The DOHBC is expected to pose a low hazard to groundwater transport due to low solubility and high log Kow, and will not pose a hazard to surface or drinking water. Partition to the atmosphere from water or wet surfaces is expected to be moderate based upon a predicted Henry's Law constant of 9.32×10^{-3} atm-m^3/mol. Vaporization from dry surfaces is a major fate,

and DOHBC is expected to exist in the atmosphere primarily as a vapor. Tendency to bioaccumulate is moderate based upon a predicted log Kow of 4.38.

7.10.2.9.2 Ecotoxicity

The USEPA's ECOSAR program models DOHBC as an ester. The predicted 96-hour EC_{50} in green algae is 1.04 mg/L, the 48-hour LC_{50} in *Daphnia* is 3.57 mg/L, and the 96-hour LC_{50} in fish is
2.22 mg/L. The predicted 14-day LC_{50} for earthworms is 906 mg/L.

7.10.2.9.3 Degradation and Treatment

The DOHBC is predicted to not be biodegradable and will be recalcitrant in the environment. Molecules in the vapor phase will be subject to degradation by hydroxyl radicals with a half-time of 38 hours.

The DOHBC will be significantly removed (85%) from waste streams by physical wastewater treatment processes, primarily by sludge adsorption (35%) and air stripping (49%).

8 DISCUSSION

8.1 Compound Summaries

8.1.1 2-(Difluoroiodomethyl)-2,3,3-trifluorooxirane [FIFO]

The FIFO is predicted to have low acute toxicity via the oral, inhalation, and dermal routes of exposure. Occupational health hazards appear to be moderate and should be within the capabilities of standard chemical material handling protection. The FIFO is not predicted to be a developmental or reproductive toxicant. The FIFO is possibly genotoxic or carcinogenic, but testing will be necessary to determine if this is accurate. The halogenated moieties of this organic molecule suggest that bioaccumulation and environmental persistence is a concern.

Ecotoxicity is predicted to be low, but FIFO is relatively long-lived in the environment, and not readily susceptible to environmental degradation pathways.

8.1.2 4,4'-(Perfluoropropane-2,2-diyl)bis(2-fluorophenol) [PFBFP]

The PFBFP is predicted to be highly toxic via oral exposure, but virtually non-toxic by inhalation or dermal exposure. This inconsistency cannot be resolved by the current modeling results, but is perhaps a reflection of poor fit of the compound with the QSAR training set. Occupational health hazards are low, but eye protection should be worn when handling the chemical. It is not clear if PFBFP is either genotoxic or carcinogenic, and further testing will be necessary to resolve this question. The PFBFP is highly resistant to biodegradation and is predicted to be recalcitrant in the environment and bioaccumulate *in vivo*.

Ecotoxicity is high and PFBFP is not degraded in the environment, and is therefore an environmental hazard, even though transportability is likely to be limited.

8.1.3 4,4'-(Perfluoropropane-2,2-diyl)phenol [BPAF]

Acute toxicity of BPAF is low. Occupational exposure hazards are moderate, with BPAF being a known dermal and ocular irritant. The BPAF is known to bind with estrogen receptors, possibly being a factor in endocrine-driven disease processes such as breast cancer; however, BPAF is not known to be mutagenic, and is not considered a carcinogen.

Ecotoxicity is largely unknown, but hazard to aquatic species is high. Recalcitrance in the environment is a concern for long-term health of ecosystems.

8.1.4 5,5'-((((Perfluoropropane-2,2-diyl)bis(4,1-phenylene))bis(oxy))bis(difluoromethylene))bis(4,4-difluoro-1,3-dioxolan-2-one) [Dioxolan]

No experimental data were found for dioxolan, and accuracy of predictions from QSAR models is expected to be poor due to dataset limitations. Therefore, it will be necessary to perform experimental tests. Available predictions suggest that dioxolan will be highly toxic and bioaccumulate in mammalian species, including humans, if ingested. Reliable estimates for LD_{50} and endpoint similar values cannot be obtained. Occupational health hazards to skin and eyes are expected to be moderate.

Ecotoxicity is expected to be limited by the solubility of dioxolan in water, but ecological effects at saturation are unknown. Environmental recalcitrance of dioxolan is of concern.

8.1.5 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diyl bis(4-methylbenzenesulfonate) [OFMBS]

The OFMBS is predicted to be highly toxic via all forms of exposure, although due to lack of volatility and solubility, the hazards of exposure are expected to be low if exposure is prevented. OFMBS likely presents an occupational exposure hazard to skin and eyes, and could be a developmental/reproductive toxicant. The compound will probably test positive in the Ames assay. The halogenated moieties of this organic molecule suggest that bioaccumulation and environmental persistence is a concern.

Ecotoxicity is also expected to be high, but is limited by the insolubility of OFMBS.

8.1.6 1,6-Diazido-2,2,3,3,4,4,5,5-octafluorohexane [DAOFH]

No experimental data were found for DAOFH, and accuracy of predictions from QSAR models is expected to be poor due to dataset limitations. Experimental testing of DAOFH is recommended to better assess toxicity. The DAOFH is predicted to moderately toxic upon ingestion, but non-toxic via inhalation. Occupational health hazards to skin and eyes are expected to be moderate. The DAOFH may test positive in the Ames assay, and may be a developmental or reproductive toxicant. The halogenated moieties of this organic molecule suggest that bioaccumulation and environmental persistence is a concern.

Ecotoxicity is expected to be limited by the solubility of DAOFH in water, but ecological effects at saturation are unknown. Environmental recalcitrance of DAOFH is of concern.

8.1.7 2,2,3,3,3,4,4,5,5-Octafluorohexane-1,6-diamine [OFHDA]

The OFHDA is predicted to be of moderate toxicity via oral ingestion, but low toxicity via the inhalation route of exposure. However, OFHDA is expected to bioaccumulate and be persistent in the environment. Occupational hazard is moderate, with dermal and ocular irritation predicted to be the primary hazards. The OFHDA is not expected to be a developmental/reproductive toxicant and is not predicted to be mutagenic.

Ecotoxicity is low, but the compound is environmentally persistent.

8.1.8 Diethyl (2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(carbonate) [DOHBC]

The DOHBC is moderately toxic via ingestion, and is predicted to have low toxicity by inhalation. Occupational exposure hazards are predicted to be relatively low, with no ocular irritation prediction possible. The DOHBC may be a developmental/reproductive toxicant. While the Ames test is predicted to be negative, the carcinogenicity prediction is moderately positive. This substance is also likely to bioaccumulate.

Ecotoxicity just passes the criteria for low; however, DOHBC is predicted to be recalcitrant in the environment; itself a concern.

8.2 Regulations and Standards

8.2.1 2-(Difluoroiodomethyl)-2,3,3-trifluorooxirane [FIFO]

No regulations or standards specific to FIFO were found. The compound may be subject to regulation in the future as a fluorocarbon.

8.2.2 4,4’-(Perfluoropropane-2,2-diyl)bis(2-fluorophenol) [PFBFP]

No regulations or standards specific to PFBFP were found. The compound may be subject to regulation in the future as a fluorocarbon.

8.2.3 4,4’-(Perfluoropropane-2,2-diyl)phenol [BPAF]

The BPAF is listed under Right-to-Know legislation in Pennsylvania and New Jersey. The BPAF is not listed under California Proposition 65 (Sigma 2014).

8.2.4 5,5'-((((Perfluoropropane-2,2-diyl)bis(4,1-phenylene))bis(oxy))bis(difluoromethylene))bis(4,4-difluoro-1,3-dioxolan-2-one) [Dioxolan]

No regulations or standards pertaining to dioxolan were found.

8.2.5 2,2,3,3,4,4,5,5-Octafluorohexane-1,6-diyl bis(4-methylbenzenesulfonate) [OFMBS]

No regulations or standards pertaining to OFMBS were found.

8.2.6 1,6-Diazido-2,2,3,3,4,4,5,5-octafluorohexane [DAOFH]

No regulations or standards pertaining to DAOFH were found.

8.2.7 2,2,3,3,3,4,4,5,5-Octafluorohexane-1,6-diamine [OFHDA]

No regulations or standards pertaining to OFHDA were found.

8.2.8 Diethyl (2,2,3,3,4,4,5,5-octafluorohexane-1,6-diyl)bis(carbonate) [DOHBC]

No regulations or standards pertaining to DOHBC were found.

8.3 Conclusions

Because many of the compounds being considered are poorly represented in the QSAR training sets, confidence in the modeling predictions is lower than desirable; however, some indication of toxicity and physical behavior can be deduced from the predictions. Most of the compounds under consideration appear to have low oral and inhalation toxicity and to not pose an unusual hazard from occupational exposure to skin and eyes. Many of the compounds under consideration are predicted to be possible developmental or reproductive toxicants by the TOPKAT program. Compounds that are structurally similar to bisphenol A (i.e., BPAF and PFBFP) are at least potential endocrine disruptors due to their predicted interactions with endocrine receptors. Genotoxicity predictions are generally favorable; carcinogenicity predictions are generally indeterminate, which is not uncommon.

Acute aquatic toxicity is predicted to be low for FIFO, Dioxolan, DAOFH, OFHDA, and DOHBC. Most compounds under consideration have limited solubility in aqueous systems, reducing the hazard to transport in groundwater, surface, and drinking water and toxicity toward aquatic species. However, all compounds under consideration with the exception of FIFO and OFHDA are predicted to be recalcitrant in the environment, which is a concern. The FIFO and OFHDA are slowly biodegraded in the environment. The UV-generated hydroxyl radicals will not degrade most of these compounds in the atmosphere due to their limited volatility. Most of these fluorinated organics are expected to bioaccumulate making initial comparisons using acute toxicity estimates limited.

Higher order polymers of these monomers are not expected to exhibit toxicity to either humans or environmental receptors due to lack of bioavailability, and hence exposure. Bioaccumulation by aquatic species is also not expected to be significant; however, persistence in the environment is likely significant due to lack of solubility and biodegradability.

9 RECOMMENDATIONS

Candidates selected for further development should receive a minimum battery of *in vitro* testing, to include the Ames mutagenicity test, an aquatic toxicity test (Microtox), and skin sensitization testing. Laboratory testing for biodegradability and soil leachability is also highly desirable.

10 POINT OF CONTACT

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U.S. Army Public Health Center
Toxicology Directorate
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APPENDIX A

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APPENDIX B

GLOBALLY HARMONIZED SYSTEM

The 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 U.N. General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

While there are several aspects of the GHS, the one most important area for our purposes is classification of chemicals into various hazard categories based upon their effects and the route of exposure. Tabular extracts of the criteria for acute toxicity (both oral and inhalation), dermal, and ocular effects are included below. More information can be found in the original source (OSHA 2012).

Table B-1. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2000	Criteria: -Anticipated LD50 between 2000 and 5000 mg/kg -Indication of significant effects in humans. -Any mortality in Category 4 -Significant clinical signs in Category 4 -Indications from other studies. *If assignment to a more hazardous class is not warranted.
Dermal (mg/kg)	≤50	>50 ≤200	>200 ≤1000	>1000 ≤2000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2500	>2500 ≤5000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts & Mists (mg/L)	≤0.05	>0.05 ≤0.5	>0.5 ≤1.0	>1.0 ≤5	

Table B-2. GHS Skin Corrosion/Irritation

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

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

Table B-3. GHS Eye Effects

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

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

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

Table B-4. GHS Acute and Chronic Aquatic Toxicity

Acute Category I **Acute toxicity ≤ 1.00 mg/L**	**Acute Category II** **Acute toxicity > 1.00 but ≤10.0 mg/L**	**Acute Category III** **Acute toxicity > 10.0 but < 100 mg/L**	
Chronic Category I Acute toxicity ≤ 1.00 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500.	Chronic Category II Acute toxicity > 1.00 mg/L but ≤ 10.0 mg/L and lack of rapid biodegradability, and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.	Chronic Category III Acute toxicity > 10.0 mg/L but ≤ 100.0 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.	Chronic Category IV Acute toxicity > 100.0 mg/L and lack of rapid biodegradability and log Kow ≥ 4, unless BCF < 500 and unless chronic toxicity > 1 mg/L.

Glossary

APHC
U.S. Army Public Health Center

AR
Army Regulation

BCF
Bioconcentration Factor

CAS RN
Chemical Abstracts Service Registry Number

EC_{50}
Effective concentration to achieve 50% effect

ER
estrogen receptor

ERR
estrogen related receptor

ESOH
Environment, safety, and occupational health

g/m^3-hour
grams per cubic meter per hour

GHS
Globally Harmonized System

LC_{50}
Concentration resulting in 50% mortality

LH
Luteinizing hormone

LOAEL
Lowest observed adverse effect level

mg/kg-day
Milligrams per kilogram per day

µM
Micromol

NTP
National Toxicology Program

ROS
Reactive oxygen species

RDT&E
Research, Development, Testing, and Evaluation

SDS
Safety data sheets

SERDP
Strategic Environmental Research and Development Program

USEPA
U.S. Environmental Protection Agency

VOC
volatile organic compound