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Toxicology Assessment for Safer Alternatives For Readiness (SAFR) Securing the Availability of Green, Enhanced Coatings (SAGE) 20-04-Infrared Colorful and Responsive Green Coating - Xanthommatin

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14. ABSTRACT
Xanthommatin (Xa) is a natural pigment found in insect and crustacean exoskeletons that is proposed as a colorant for paints and coatings of military interest. The Army Public Health Center evaluated the toxicity of Xa using *in silico* and *in vitro* approaches, as well as a literature review and toxicity assessment of Xa to identify environmental and human health hazards. The Xa is not predicted to be an environmental or ecological hazard. The Xa was negative in the Ames assay for bacterial mutagenicity. Based on *in vitro* testing and *in silico* modeling, Xa is predicted to be a skin sensitizer; however, the potency of Xa was not characterized. It is recommended that additional skin sensitization testing be conducted to reduce uncertainty of this occupational hazard.

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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 are vital to the readiness of the U.S. Army. Safeguarding the health of Soldiers, Civilians, and the environment requires an assessment of alternatives before they are fielded. Continuous assessments begun early in the Research, Development, Testing, and Evaluation (RDT&E) process can save significant time and effort during RDT&E, as well as over the life cycle of the items developed. Residues of pyrotechnics, propellants, explosives, and coatings 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 Department of Defense (DoD) millions of dollars and can interfere with training activities.

1.2 Purpose

This project seeks to test and qualify Xa, a biologically derived pigment proposed as a colorant for coatings and other applications. Xanthommatin will eliminate the use of more hazardous colorants resulting in a product with reduced human health and environmental impact. The role of the U.S. Army Public Health Center (APHC) in preparing this Toxicology Assessment is to determine the human health and environmental hazards of Xa and provide recommendations for usage.

1.3 Conclusions

Xanthommatin was evaluated using *in silico* and *in vitro* approaches to estimate toxicological hazard. The acute toxicity of Xa is predicted to be low for oral and dermal exposures; however, it is predicted to be a potential inhalation hazard. Xanthommatin was not mutagenic it had low aquatic toxicity and was negative in estrogen and androgen screens for endocrine disruption. As a naturally occurring pigment, Xa is expected to have minimal ecological toxicity. Xanthommatin is modeled to be a weak skin sensitizer and these data were supported by testing in *in vitro* assays for skin sensitization.

1.4 Recommendations

Preliminary toxicity evaluation for Xa suggests relatively low toxicity via dermal and oral routes of exposure and negligible hazards from environmental releases. Continued development of Xa for use in military applications is recommended. It is further recommended that Xa be evaluated for inhalation toxicity if its use involves respiratory exposures. As Xa may have cosmetics applications it is important that further testing is conducted to better characterize the skin hazards of Xa. Individuals that handle Xa should use appropriate Personal Protective Equipment to eliminate dermal exposures.

2 REFERENCES AND GLOSSARY

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. W74RDV90166292. 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, 2007 (Department of the Army (DA) 2007);
- AR 40-5, Preventive Medicine, 2020 (DA 2020);
- AR 70-1, Army Acquisition Policy, 2018 (DA 2018);
- Department of Defense Instruction 4715.23 (DoDI 2018); and
- Army Environmental Requirement and Technology Assessment requirement PP-13-12-03, Securing the Availability of Green, Enhanced (SAGE) Coatings (AERTA 2018) and PP-4-02-05, Alternative Products in Cleaning and Degreasing Processes.

The Sponsor is the DEVCOM, SAFR Program. The Principle Investigator is Dr. Richard Osgood, DEVCOM Soldier Center, Natick Massachusetts.

4 BACKGROUND

Current regulations require assessment of human health and environmental (soil, surface water, and groundwater) effects arising from exposure to substances under consideration for Army acquisition. 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, APHC has been engaged with creating a phased process to identify ESOH effects impacting readiness, training, and development costs (APHC 2021). This report represents the status of information available for this work unit as of the date of publication.

Xanthommatin is a naturally occurring ommochrome pigment found in arthropods and cephalopods (Figon and Casas 2019). Ommochromes are widely occurring pigments and have a role in compound eye vision and color patterning in cephalopod skin (Williams et al. 2019b). At present, Xa is not available commercially, but it can be chemically synthesized via electrochemical oxidation of the Xa precursor. Xanthommatin synthesis is challenged by scalability and purity issues; efforts are underway to improve the production process of Xa (Williams et al. 2019a).

5 STATEMENT OF THE PROBLEM

Xanthommatin is proposed for use in military applications that do not require the use of urethanes or isocyanates. The toxicological hazards of Xa are not known and must be evaluated during the RDT&E process to ensure that Xa hazards are known prior to acquisition and fielding.

6 METHODS

In order to determine the human health and environmental impact of Xa, it is necessary to correctly identify it and determine its physical, chemical, and toxicological properties. Xanthommatin Chemical Abstracts Service Registry Number (CASRN) is 521-58-4. 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. Xanthommatin Simplified Molecular Input Line Entry System (SMILES) was captured from PubChem and used to generate the physicochemical properties with EPI Suite (Estimation Programs Interface (EPI) Suite™) (U.S. Environmental Protection Agency (EPA) 2015b, PubChem 2020).

The properties necessary to assess environmental fate and transport include:

- Molecular weight (MW) (in g per mol; g/mol).
- Boiling point (bp) in °C.
- Octanol-water partition coefficient (log K_{OW}).
- Organic carbon partition coefficient (log K_{OC}).
- Water solubility (mg/L or mL/L).
- Henry’s Law constant (K_H).
- Vapor pressure (vp) in mm of mercury (Hg) – mmHg.

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

Toxicological information needed to estimate potential human health risks includes reported toxicity effects of oral, inhalation, dermal, and ocular exposures; potential for developmental or reproductive toxicity, neurotoxicity, genotoxicity, carcinogenicity; and mode(s) and mechanisms of toxicity. Values reported herein include LD_{50} (reported in mg/kg), no-observed-adverse-effect level (or concentration) (NOAEL/C), lowest-observed-adverse-effect level (or concentration) (LOAEL/C), no observed effect level (or concentration) (NOEL/C), lowest observed effect level (or concentration) (LOEL/C). Reported in mg/kg or mg/L, median effect concentration (EC_{50}), median inhibitory concentration (IC_{50}), median lethal concentration (LC_{50}) typically reported as mass (g or mg) per cubic meter (m^3) or mg/L, clinical chemistry values may be reported in dL and some water quality values may be reported in µg/L or ppm.

Toxicological information was derived directly from primary sources whenever possible. Where data gaps exist, *in silico* toxicity estimates were made using Quality Structure-activity Relationship (QSAR) programs: TOPKAT® (Toxicity Prediction Komputer Assisted Technology) (BIOVIA 2021), DEREK (Deductive Estimation of Risk from Existing Knowledge) (DEREK 2022) and ECOSAR™ (ECOlogical Structure Activity Relationship) (EPA 2015). Data acquired from the TOPKAT models provides confidence and goodness-of-fit information for each endpoint so that qualitative estimates and comparisons between chemicals can be given. Skin sensitization data acquired from the DEREK model was used to supplement the TOPKAT results. The ECOSAR program provides point estimates for aquatic endpoints (green algae, *Daphnia*, and fathead minnow acute toxicity and chronic values).

Sources used in this search included The Merck Index (O'Neil 2006); the National Institutes of Health (NIH), the EPA, the U.S. Department of Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR), the EPA ECOTOXicology Database System (ECOTOX; (ECOTOX 2009)), and the Defense Technical Information Center. Additional sources may include publications from the U.S. National Institute for Occupational Safety and Health (NIOSH), the World Health Organization, and the International Agency for Research on Cancer (IARC). Primary references are identified and retrieved by PubMed® and the APHC interlibrary loan service.

Persistence, bioaccumulation, human health toxicity, and ecotoxicity were assigned to general risk categories (low, moderate, or high) using defined criteria modified from the previously published work of Howe et al. (2007). Appendix B, Table B-1 describes the criteria used in the categorical definitions of risk. Where applicable, the Global Harmonized System (GHS) is also used to categorize risk; additional information is found in Appendix B, Section B-2 through B-7. If no experimental data were identified from the literature, then the QSAR estimates were used.

7 RESULTS

7.1 Physicochemical Properties

Xanthommatin physicochemical properties that are relevant for evaluating toxicity and environmental fate are summarized in Table 1. Physical properties include melting/boiling points and molecular weight; solvation properties include phase partitioning and solubility. The primary sources for these properties include PubChem®, Safety Data Sheets (SDS) (when available), and EPISuites (when experimentally measured data were not available).

Table 1. Physicochemical Properties of Xa

PROPERTY	VALUE	PROPERTY	VALUE
Molar Mass	423.34 g/mol	**Log Kow**	-2.40
Melting point	339.13 °C	**Log Koc**	3.046
Boiling point	720.45 °C	**Henry's Law Constant**	1.46E-28 atmosphere/m^3-mol
Solubility	2,091 mg/L	**Vapor Pressure**	1.27 E-15 millimeters Mercury @ 25 °C
Rapid biodegradation	No, ½ life days-weeks	**Atmospheric oxidation**	High, ½ life <1 hour
Log BCF	0.5 L/kg wet weight	**Biotransformation**	½ life 16.9 minutes
Chemical classes	aliphatic amines-acid, vinyl/allyl ketones-acid, vinyl/allyl ethers-acid		

Legend:
°C = degrees Celsius
g/mol = gram/mol (1 mol = 6.0221408E+23 molecules)
mg/L = milligram/liter
L/kg = liters/kilogram

7.2 Xanthommatin (Xa) [CASRN: 521-58-4]

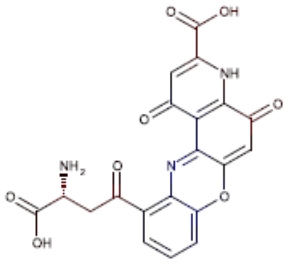

Figure 1. Xanthommatin

7.2.1 General Information

Xanthommatin (Figure 1) is a naturally derived brown pigment found in the eyes and shells of most insects. It is a polycyclic heteroarene in the "pyridophenoxazine" chromophore family (Figon and Casas 2019). It is the principle ommochrome. Ommochromes are generated from tryptophan catabolism and are known to mediate compound eye vision as well as reversible and irreversible color patterning. Xanthommatin can also be synthesized artificially. The Xa product tested at APHC was synthetic.

7.2.2 Toxicity data

7.2.2.1 Oral

No toxicity data were identified. By QSAR, the predicted LD_{50} for Xa was 528.3 mg/kg. Using a Cell-based Acute Oral Toxicity Estimate (CAOTE) algorithm the LD_{50} was estimated as > 2,000 mg/kg (APHC 2022). The APHC used CAOTE to analyze the *in vitro* cytotoxicity data from Deravi et al (2022); the data suggest the LD_{50} is greater than 3,500 mg/kg and supports a weight of evidence that Xa has low oral toxicity. Using these data for the GHS system Xa would be GHS Category 4/5 for oral toxicity.

7.2.2.2 Inhalation

No toxicity data were identified. The TOPKAT predicted LC_{50} for Xa is 140 mg/m^3-hour. Using the GHS system, Xa is GHS Category 2 for inhalation toxicity.

7.2.2.3 Dermal

No toxicity data were identified. A QSAR model for acute dermal toxicity is not available. Based on Xa molecular weight and natural product classification it is unlikely to be acutely toxic via dermal exposure. Using QSAR, Xa is predicted to be non-irritating. Both TOPKAT and DEREK predict Xa is a weak sensitizer. Xa was negative for sensitization in the *in vitro* human-cell line activation test h-CLAT and positive for sensitization in the Direct Peptide Reactivity Assay (DPRA) (APHC 2022). Using a weight of evidence, Xa is a predicted to be a weak sensitizer.

7.2.2.4 Ocular

No toxicity data were identified. Using TOPKAT, Xa is predicted to be a mild eye irritant.

7.2.2.5 Development and Reproduction

No data for reproductive/developmental toxicity were found. TOPKAT estimates were negative for developmental toxicity. Xa was screened for endocrine disruption activity and was found negative in *in vitro* estrogen and androgen agonist and antagonist tests up to 31.25 µM (Deravi et al. 2022).

7.2.2.6 Genotoxicity

In vitro testing of Xa was performed by APHC to screen for DNA damage using bacteria cells (APHC 2022). Xanthommatin was negative in the fluctuation Ames assay with *Salmonella typhimurium* TA100 with and without liver metabolic S9. Marginal cytotoxicity was observed at 2,000 µg/mL (the highest tested concentration). In a separate test, *S. typhimurium* test strains TA98, TA535, TA1537, TA100, and *E.coli* WP2 uvrA were exposed to Xanthommatin at levels of 31.6 µg/plate to 5,000 µg/plate for 48 hours (Deravi et al. 2022). All results were negative for mutations, either with or without S9 microsomal activation (Deravi et al. 2022).

7.2.2.7 Carcinogenicity

No animal data were identified. Using TOPKAT, Xa was predicted to be non-carcinogenic with high confidence. It has been proposed that Xa may provide UV protection and have use in sunscreens as an antioxidant (Wilson et al. 2022).

7.2.2.8 Neurotoxicity

No data were available. Xanthommatin is a product of the kynurenine tryptophan oxidation pathway that may also contribute to the synthesis of serotonin and melatonin (Han et al. 2007). There is no evidence that Xa would be neuroactive; however, there are indications that endogenous Xa and other products of the kynurenine pathway are involved in oxidative stress and when dysregulated may have pathophysiological effects (Zhuravlev et al. 2016). Using QSAR, Xa is not expected to cross the blood-brain barrier, which reduces the likelihood of neurological effects.

7.2.2.9 Mode/Mechanism of Action

Xanthommatin was inactive in the National Cancer Institute *in vivo* anticancer drug screen (PubChem 2020). Xanthommatin is a phenoxazinone pigment responsible for brown coloration and is derived from tryptophan through a series of enzymatic steps (Yamamoto et al. 1976). In insects, approximately 30% of tryptophan is converted to Xa (Chan-Higuera et al. 2019). Xanthommatin has been shown to have both pro- and antioxidant properties (Chan-Higuera et al. 2019). Using QSAR, the Absorption, Distribution, Metabolism, and Elimination (ADME) predictions suggest Xa has a very poor intestinal absorption profile. Xanthommatin that is absorbed via the gut is predicted to be non-toxic to the liver and Xa does not inhibit cytochrome P450 2D6 (CYP2D6), a human enzyme involved in drug metabolism. The QSAR-ADME predicts Xa will have a solubility similar to many drugs and will circulate freely in blood. Based on modeling results, Xa is not likely to bind to plasma proteins so liver clearance of this compound should not be impacted.

7.2.3 Ecological Data

7.2.3.1 Fate and Transport

Using EPISuites, based on predicted water solubility of >2 g/L and a log K_{OC} of 3.046, Xa is predicted to moderately bind to soil and be a moderate to low transport risk into ground water. In air, Xa would exist predominantly bound to particulates and any free unbound Xa is expected to oxidize rapidly, with a ½ life of 22 hours- the particulate-sorbed fraction may be resistant to atmospheric oxidation. Xanthommatin is not volatile and has a very low K_H (1.46E-28 atm/m^3-mol) indicating it will not volatilize from rivers or lakes. Xanthommatin is not expected to bioaccumulate (Log BCF=0.5 L/kg wet-weight) and is expected to be rapidly metabolized with a biotransformation half-life of 16.9 minutes.

7.2.3.2 Ecotoxicity

Xanthommatin was modeled with three different class-specific estimates: Aliphatic amines-acid, vinyl/allyl ketones-acid and vinyl/allyl ethers-acid. All but the vinyl/allyl ethers acids prediction for acute toxicity in fish were orders of magnitude above the solubility limit. The EPISuites and TOPKAT predict the aquatic toxicity of Xa is low to fish and TOPKAT predicts it is moderately toxic to daphnia (80.7 mg/L). As Xa is a pigment found in aquatic invertebrates, the confidence in the TOPKAT estimate is low. No models for terrestrial receptors were available. Based on the structure of Xa, it is not expected to be toxic to plants and it is a dietary constituent for insectivores.

Army Public Health Center tested Xa in the Microtox™ assay – a surrogate assay for the 96-hour fathead minnow acute toxicity test (APHC 2022). The Xa EC_{50} in the Microtox test was >2000 mg/L and is categorized as 'relatively harmless' using EPA hazard categories and is considered to have little to no toxicity in GHS (i.e., insufficient toxicity to warrant classification).

7.2.3.3 Degradation/Treatment

Xanthommatin is expected to not persistent in the environment (1/2 life days to weeks) and may be subject to photodegradation in air. The fugacity model suggests Xa will partition predominately to soil (83.2%) and water (16.2%) with very little Xa (<1%) remaining in air or sediment. EPISuites and TOPKAT predict Xa undergoes aerobic biodegradation but will not extensively degrade in waste water treatment plants (<2%).

8 DISCUSSION

8.1 Compound Summary

The data presented in section 7.2 are summarized in Table 1. The final hazard characterization also incorporates assessment of the uncertainty associated with available data and the nature of potential exposure associated with use of Xa.

Table 2. *In silico* and *in vitro* Assessment of Xanthommatin

ANALYSIS TYPE	TOXICITY ENDPOINT	XANTHOMMATIN		
		VALUE	HAZARD	CONFIDENCE
QSAR-Discovery Studio-TOPKAT	Rat Oral LD_{50}	528 mg/kg	GHS 4	very low
	Rat Chronic LOAEL; mg/kg-day	20 mg/kg-day		very low
	Rat Inhalational LC50 g/m^3	0.14 g/m^3-hour	GHS 2	very low
	Skin Irritancy	negative	NC	very low
	Skin Sensitization	weak positive	GHS 1	very low
	Ocular Irritancy	mild irritant	GHS 2b	low
	Developmental Toxicity Potential	negative		very low
	Ames Mutagenicity	negative		moderate

	Weight of Evidence Carcinogenicity	**negative**		moderate-high
	Aerobic Biodegradability	**positive**		very low
	Fathead Minnow LC_{50}	**2427 mg/L**	**GHS-NC**	very low
	Daphnia EC_{50}	**81 mg/L**	**GHS 3**	very low
ECOSAR	**Fathead Minnow LC_{50}**	**>10,000 mg/L**	**GHS-NC**	n/a
	Daphnia EC_{50}	**>10,000 mg/L**	**GHS-NC**	n/a
	Green Algae EC_{50}	**>10,000 mg/L**	**GHS-NC**	n/a
IN VITRO	**Rat Oral LD_{50} (CAOTE)**	**>2000 mg/kg**	**GHS 5**	moderate
	Ames Mutagenicity	**TA100 (-/+S9)**		high
	Skin Sensitization	**+DPRA/-hCLAT**	**GHS 1 (weak sensitizer)**	moderate
	Fathead Minnow LC_{50}	**>2000 mg/L**	**GHS-NC**	high

Legend:
LD_{50} = median lethal dose
LOAEL = lowest observed adverse effect level
LC_{50} = median lethal concentration
EC_{50} = median concentration of effect
CAOTE = cell-based approximate oral toxicity estimate
h-CLAT = human cell line activation test
DPRA = direct peptide reactivity assay
GHS = global harmonized system
NC = not categorized (insufficient toxicity for classification)
TA100 (-/+S9)= Salmonella tester strain with and without S9 microsomes
mg/kg = milligram/kilogram

Hazard color key		Highest		Moderate		Low to negligible

8.2 Regulations and Standards

No regulations or standards are available for Xa. Xanthommatin is commercially unavailable.

9 RECOMMENDATION

Based on physical and chemical properties and limited empirical data, the toxicity evaluation for Xa suggests relatively low toxicity via dermal and oral routes of exposure. Hazards from environmental releases are expected to be low, as well. Continued development of Xa as a constituent of paint formulations is recommended. Xanthommatin is expected to have low ecological toxicity. Toxicity data were not identified for most mammalian endpoints of interest; however, there have been recent publications evaluating bacterial mutagenicity and endocrine disruption (Deravi et al. 2022). Army Public Health Center conducted *in silico* and *in vitro* toxicity assessments of Xa (APHC 2022). Xanthommatin evaluations using *in silico* approaches were hampered by Xa having several structural parameters that were outside of the optimum prediction space or novel. Xanthommatin was negative for bacterial mutagenicity and skin irritation but showed conflicting results in tests for skin sensitization (APHC 2022). Computer

modeling suggested that Xa is a weak skin sensitizer. Due to the weight of evidence that Xa may be a skin sensitizer, it is highly recommended that additional skin sensitization testing be conducted. In consideration of its score as a weak sensitizer and indications that Xa may have cosmetic applications, it is recommended that human volunteer patch testing be conducted. If Xa use will involve inhalation exposure, then it is recommended that respiratory toxicity be evaluated.

10 POINT OF CONTACT

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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

	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	

Source: Modified from Howe, et al. 2007

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} = median effective concentration
µg/L = micrograms per liter

B-2 GLOBALLY HARMONIZED SYSTEM

GHS is the acronym for the Globally Harmonized System of Classification and Labeling of Chemicals. The GHS attempts to establish international consensus for defining health, physical, and environmental hazards of chemicals; creating a classification process for comparison with defined hazard criteria; and communicating hazard information and protective measures on labels and Safety Data Sheets (SDS, formerly known as Material Safety Data Sheets, MSDS). The GHS attempts to reduce differences among levels of protection for workers established by the different countries and reduce regulatory burden and barriers to commerce while establishing consistent standards for classification. The GHS is the result of an international mandate adopted in the 1992 United Conference on Environment and Development, often called the "Earth Summit." The harmonization and classification of chemicals was one of six program areas endorsed by the U.N. General Assembly to strengthen international efforts in the environmentally sound management of chemicals.

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

Table B-2. GHS Acute Toxicity

	Category 1	Category 2	Category 3	Category 4	Category 5
Oral (mg/kg)	≤5	>5 ≤50	>50 ≤300	>300 ≤2,000	Criteria: -Anticipated LD_{50} between 2,000 and 5,000 mg/kg -Indication of significant effects in humans. -Any mortality in Category 4 -Significant clinical signs in Category 4 -Indications from other studies. *If assignment to a more hazardous class is not warranted.
Dermal (mg/kg)	≤50	>50 ≤200	>200 ≤1,000	>1,000 ≤2,000	
Gases (ppm)	≤100	>100 ≤500	>500 ≤2,500	>2,500 ≤5,000	
Vapors (mg/L)	≤0.5	>0.5 ≤2.0	>2.0 ≤10	>10 ≤20	
Dusts & 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.					

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 1	**Category 2**	**Category 3**		**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 1	**Category 2**	**Category 3**	**Category 4**	**Not Categorized**
Acute Cat I and log Kow ≥ 4, unless BCF < 500; Or chronic toxicity ≤ 0.01 mg/L	Acute Cat II and log Kow ≥ 4, unless BCF < 500; Or chronic toxicity 0.01-0.1 mg/L .	Acute Cat III and log Kow ≥ 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 Kow ≥ 4, unless BCF < 500; Or chronic toxicity > 1.0 mg/L	Acute toxicity >100 mg/L, Log Kow < 4, BCF< 500 and chronic toxicity > 1.0 mg/L

Legend:
mg/L = milligrams per liter
BCF = Bioconcentration factor

Table B-6. GHS Carcinogenicity Categories

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.

GLOSSARY

APHC
Army Public Health Center

atm
standard unit of atmospheric pressure

ATSDR
Agency for Toxic Substances and Disease Registry

BCF
bioconcentration factor

bp
boiling point

ºC
degrees Celsius

CASRN
Chemical Abstracts Service Registry Number

CCDC
U.S. Army Combat Capabilities and Development Command

DEREK
Deductive Estimation of Risk from Existing Knowledge

ECOSAR
Ecological Structure Activity Relationship

ECOTOX
USEPA ECOTOXicology Knowledgebase

EC_{50}
median (50%) effect concentration

EPA
U.S. Environmental Protection Agency

EPISuite
Estimation Programs Interface Suite™

ESOH
environmental safety and occupational health

GHS
Global Harmonization System

K_H
Henry's law constant

IARC
International Agency for Research on Cancer

IC_{50}
median (50%) inhibitory concentration

kg-day
kilogram per day

kg
kilogram

L
liter

LC_{50}
median (50%) lethal concentration

LD_{50}
median (50%) lethal dose

log K_{OC}
Log organic carbon partition coefficient

log K_{OW}
Log octanol-water partition coefficient

LOAEC
lowest observed adverse effect concentration

LOAEL
lowest observed adverse effect level

LOEC
lowest observed effect concentration

m^3
cubic meters

µg
microgram

mg
milligram

mL
milliliter

mm Hg
millimeter of mercury

mol
mole; $6.022x10^{23}$ particles

MSDS
Material Safety Data Sheets

MW
molecular weight

n/a
not applicable

NIH
National Institutes of Health

NIOSH
U.S. National Institute for Occupational Safety and Health

NOAEC
no observed adverse effect concentration

NOAEL
no observed adverse effect level

NOEC
no observed effect concentration

NOEL
no observed effect level

NTP
National Toxicology Program

OECD
Organization for Economic Co-operation and Development

OSHA
Occupational Safety and Health Administration

PEL
permissible exposure limit

ppm
parts per million

QSAR
quantitative structure-activity relationship

RDT&E
Research, Development, Test and Evaluation

SAFR
Safer Alternatives for Readiness

SDS
Safety Data Sheet

SMILES
simplified molecular-input line-entry system

TOPKAT
Toxicity Prediction by Komputer Assisted Technology

UV
ultraviolet

vp
vapor pressure

v/v
volume per volume

Xa
Xanthommatin