A Review of Chemical Warfare Agent Simulants for the Study of Environmental Behavior

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Abstract

There is renewed interest in the environmental fate of chemical warfare agents attributable to the intensified threat of chemical weapons use in a terrorist attack. Knowledge of processes that influence the fate of agents such as distilled mustard, lewisite, tabun, sarin, soman, and VX in the environment is important for development of disposal strategies and for risk and exposure assessments. However, it is often necessary to conduct studies examining chemical agent behavior using simulants due to the toxicity of the agents and usage restrictions. The objective of this study was to review the physical-chemical properties and mammalian toxicity of compounds that can be used to simulate chemical agents and to identify the most appropriate compounds to simulate specific environmental fate processes, including hydrolysis, sorption, bioavailability and volatilization.

Key words: warfare agent, simulant, microbial degradation, partition coefficient, toxicity

1.0 Introduction

Due to the increased threat of chemical weapons attacks by terrorist organizations, there is renewed interest in the environmental fate of chemical warfare agents (CWAs) including blister agents such as distilled mustard (HD) and lewisite (L), and nerve agents such as tabun (GA), sarin (GB), soman (GD), and VX (Figures 1-4) . Knowledge of the processes that influence the fate and transport of CWAs in the environment can aid in predictions of environmental persistence, estimates of exposure, and the development of decontamination and disposal strategies. Because CWAs are highly toxic and their use is restricted in non-surety laboratories, research on the environmental fate of CWAs is often conducted using simulant compounds [1-10].

An ideal chemical agent simulant would mimic all relevant chemical and physical properties of the agent without its associated toxicological properties. Although a number of compounds have been used as CWA simulants, no individual compound is ideal because a single simulant cannot satisfactorily represent all environmental fate properties of a given CWA. Thus, a number of different chemicals have been used as CWA simulants depending on the physical-chemical property of interest. Over twenty years ago, Bennett et al. [11] reviewed a number of simulants and reported limited environmental fate data and toxicity information for these chemicals. Although a simulant database, the Chemical Biological Agent Simulant Knowledgebase (ASK), has been recently developed by the U.S. military, this database is not available in the public domain [12]. In this review, we summarize the physical-chemical properties and the mammalian toxicity of compounds that have been used in previous studies to simulate HD, L, GA, GB, GD, and VX and identify appropriate simulants based on the environmental fate mechanism of interest.

The following section provides a review of research on the fate of specific CWAs in the environment. This is followed by a description of CWA simulants, including physical-chemical and toxicological properties as well as a comparison to those of the CWA they are intended to simulate. Finally, recommendations for appropriate CWA simulants are provided for specific environmental fate processes.

2.0 Environmental fate of chemical agents

Potential fate pathways for CWAs in the environment include volatilization, sorption, hydrolysis, photolysis and microbial degradation. There are few studies reviewing the environmental fate of CWAs [13,14], though recently, a mathematical model was used to estimate the phase partitioning and fate of CWAs in landfills [15]. Hydrolysis is the primary environmental fate mechanism for many CWAs in aqueous systems, with reported half-lives on the order of minutes to days. A hydrolysis half-life of 8.5 min has been reported for HD in aqueous systems [16]; however, the overall rate of HD disappearance is often limited by the slow rate of HD dissolution from a non-aqueous phase into water. Also, hydrolysis products can coat the surface of HD droplets and retard HD dissolution [14]. Both its hydrophobicity and the formation of hydrolysis products make non-aqueous-phase HD fairly persistent in the environment. HD hydrolysis can occur via two pathways that are dependent on water availability, but the dominant products of either pathway are thiodiglycol (TDG) and hydrochloric acid [14].

Hydrolysis of L occurs rapidly, with a half-life of 0.7 min calculated from an estimated hydrolysis rate of 1.0 min^{-1} at 20°C [17]. Because L hydrolyzes so rapidly, the toxic effects attributed to L may actually be those of its primary hydrolysis product, 2-chlorovinyl arsonous acid [18]. 2-chlorovinyl arsonous acid is transformed to lewisite oxide through dehydration [5].

Hydrolysis rates of nerve (G) agents are slower than those of HD or L, with half-lives of 14-28 h at pH 7 and 25°C, 39 h at pH 7.5 and 25°C, and 60 h at pH 6 and 25°C for GA, GB, and GD, respectively [14,19]. The primary product of GA hydrolysis is phosphoric acid and the primary product of GB and GD hydrolysis is methylphosphonic acid (MPA) [13,18]. Hydrolysis of VX is slower than that of the G-agents, with a reported half-life of 17-42 d at 25°C and pH 7 [20]. The hydrolysis products are pH-dependent, but S-(2-diisopropylaminoethyl) methyl phosphonothioate (EA2192) and ethanol are formed at pH 7 to 10 [13]. EA2192 has anticholinesterase activity that is similar to that of VX [14].

The rate of CWA hydrolysis is dependent on such factors as temperature, pH and water quality. Hydrolysis rates increase with increasing temperature. For example, the rate of HD hydrolysis at 70°C was 28 times that at 30°C [21]. For GB at pH 7, hydrolysis half-lives of 2650 h and 39-41 h were reported at 0°C and 25°C, respectively [20]. The effect of pH on CWA hydrolysis varies; e.g. GD hydrolysis is acid-catalyzed with half-lives of 3, 50, and 60 hr at pH 2, 7.6, and 9, respectively [20], while VX hydrolysis is base-catalyzed with half-lives of 2400, 17 and 0.02 d at pH 2-3, 11, and 14, respectively [20]. The hydrolysis rate of HD does not vary between pH 5 and 10 [20], however high chloride ion concentrations can inhibit HD hydrolysis [22]. GA and GB hydrolysis rates were enhanced by the presence of dissolved oxygen and cations such as Cu^{2+}, Ca^{2+}, Al^{3+}, Mg^{2+}, and Mn^{2+} [20].

Sorption processes affect environmental transport and bioavailability of CWAs. In many instances, partitioning between aqueous and solid phases is controlled by the organic carbon content of sorbents such as soils, sediments, or landfill solids. The relationship between the CWA concentration in the organic carbon fraction of a sorbent and the aqueous CWA concentration is described by K_{oc}, the organic carbon – water partition coefficient, and log K_{oc}

values for neutral organic compounds can be predicted from octanol-water partition coefficient (log K_{ow}) values. Log K_{ow} for CWAs and CWA simulants are presented in a later section. Some CWAs, such as VX, are ionizable; therefore, sorption processes will be a function of solution pH. VX is a tertiary amine (Figure 3) with a pK_a of approximately 9 [23-25]. Thus, VX exists predominantly in the cationic form at neutral pH, complicating predictions of VX sorption to environmental media [26].

Volatilization of CWAs from the aqueous phase is another factor controlling environmental fate of CWAs. Partitioning between gas and aqueous phases can be predicted using Henry's Law, and dimensionless Henry's Law (K_H) values for CWAs and CWA simulants are presented in later sections.

Although biodegradation of CWAs is theoretically possible, biodegradation of many CWAs has not been observed due to toxicity [15]. Similarly, there is little information on photodegradation rates of CWAs. Only one study was identified that measured direct photolysis of organophosphorus nerve agents. GD degradation was found to be slightly enhanced in wet air after irradiation with a mercury lamp [14]. Because HD does not absorb ultraviolet radiation above 290 nm, environmental photodegradation of this compound will be limited [15]. A study of the UV absorption spectra of chemical agents and simulants found weak absorption for HD, GA, GB, GD, and VX above 290 nm, indicating that photolysis is not an important fate pathway in the environment [27]. Some photodegradation of L may occur [27], but photodegradation rates have not been published.

3.0 CWA simulants

3.1 Distilled Mustard (HD) simulants

A variety of compounds have been used to simulate HD. Wagner and MacIver [2] and Wagner and Bartram [3] used 2-chloroethyl methyl sulfide (CEMS) and 2-chloroethyl phenyl sulfide (CEPS) to simulate HD in studies of the degradation and fate of HD in soil. Yue et al. [6] used chloroethyl ethyl sulfide (CEES), also called half-mustard (HM), to simulate HD in a study of CWA removal from water using activated carbon filters, while Singer et al. [10] used methyl salicylate (MS) to evaluate the sorption of HD to components of a furnished room. CEES has also been used to simulate HD hydrolysis [28]. In addition to the simulants discussed above, Bennett et al. [11] lists potential simulant compounds that have been used in various applications. A list of all potential simulants for HD and the associated physical and chemical properties are given in Table 1. Figure 1 shows the molecular structures of HD and potential HD simulants.

3.2 G-agent simulants

A number of potential simulants for GA, GB, and GD have been identified. Raber and McGuire [7] used diphenyl chlorophosphate (DPCP) as a simulant for G-agents in a study examining oxidative decontamination. Singer et al. [10] used three compounds, dimethyl methylphosphonate (DMMP), diethyl ethylphosphonate (DEEPT), and triethylphosphate (TEP) to evaluate the sorption of G-agents to components of a furnished room. Diisopropyl methylphosphonate (DIMP) was used as a G-agent simulant in studies evaluating the sorption of organic contaminants from water to activated carbon fibers [4,6]. Both DMMP and DIMP are listed Schedule 2 substances in the Chemical Weapons Convention (CWC), indicating that they are either sufficiently toxic to be used as a chemical weapon or are a precursor to other listed substances. Schedule 2 substances have no large-scale industrial use, but may have legitimate small-scale uses. DMMP and DIMIP production is subject to declaration to the Organization for

the Prohibition of Chemical Weapons (OPCW). In addition to the simulants discussed above, Bennett et al. [11] catalogued a number of additional G-agent simulants. Physical and chemical properties of GA, GB, GD and potential simulants are presented in Table 2. Figure 2 shows the molecular structures of G-agents and G-agent simulants that have been used in prior studies.

3.3 VX simulants

Amiton (VG) is commonly used to simulate VX [7,8]. However, VG is a listed Schedule 2 substance and retains many of the hazardous properties of VX. Additional compounds that have been used to simulate VX include O,S-diethyl phenylphosphonothioate (DEPP) and organophosphorus pesticides such as malathion and parathion [1,3,9,11]. A list of potential simulants for VX and associated physical chemical property data are shown in Table 3. Figure 3shows the molecular structures of VX and potential VX simulants.

3.4 Lewisite simulants

L rapidly transforms to lewsite oxide in the environment; therefore, previous studies investigating the fate of L in the environment have focused on lewisite oxide. Tomkins et al. [5] used phenylarsine oxide as a simulant for lewisite oxide in the development of a solid-phase microextraction-gas chromatographic analytical method for lewisite oxide in soil. The molecular structures of lewisite, lewisite oxide and phenylarsine oxide are given in Figure 4 while the corresponding physical-chemical property data are presented in Table 4.

4.0 Selection of appropriate simulants for environmental fate processes of CWAs

The selection of an appropriate simulant must be made in consideration of the intended use (i.e. sorption isotherms, biodegradation assays, or volatilization experiments), as the simulant that is most appropriate to simulate a particular environmental process may not be the best choice for all fate studies. Selection of an appropriate simulant requires evaluation of the

physical-chemical properties that most strongly affect the fate process of interest as well as the toxicity of the simulant. In this section, suggestions for simulants to study sorption/desorption, biodegradability, volatilization and hydrolysis are developed based on qualitative assessment of the physical-chemical property data and molecular structures as provided in Tables 1-3 and Figures 1-4, respectively.

4.1 Sorption/Desorption

Sorption to and subsequent desorption from the organic carbon fraction of a solid is governed primarily by the log K_{ow} values of neutral CWAs; therefore, simulant compounds with similar log K_{ow} values will exhibit the most similar sorptive behavior relative to the original CWA. A secondary criterion is that the simulants should have a molecular size similar to that of the actual CWA because (de)sorption rates are governed by diffusion of sorbates through the intraparticle polymeric matrix and/or porous structure of the sorbent. Simulants that are larger than the original agent, especially those containing aromatic functional groups, may diffuse more slowly, while simulants that are smaller than the original agent may diffuse more rapidly. Furthermore, for heterogeneous porous adsorbents such as activated carbons or chars, smaller molecules can access a larger number of adsorption sites than larger adsorbates because of steric (size exclusion) effects.

For HD (log K_{ow} 2.41 to 2.55) [29], simulants with similar log K_{ow} values include MS, CEES, diethyl pimelate, diethyl adipate, and CEMS (Table 1). Of these compounds, CEES and CEMS have the closest structure to HD, making them the best choices to simulate HD sorption. While MS has a similar log K_{ow}, it contains a phenyl group, while HD does not. Both diethyl pimelate and diethyl adipate are much larger than HD.

For the G-agents, several simulants have log K_{ow} values that are similar to the original agents (Table 2). For GA (log K_{ow} 0.394) and GB (log K_{ow} 0.3) [14], the simulants that most closely match the log K_{ow} are DEEP, TEP, and ECA. DEEP and TEP are organophosphorus compounds and fairly similar in structure to GA and GB. For GD (log K_{ow} 1.78), the simulants with the most similar log K_{ow} values are paraoxon, BUSH, DEHP, and DIMP. Although paraoxon has the log K_{ow} that is most similar to GD, it contains a large aromatic functional group, making its structure and size quite different from that of GD. Similarly, BUSH is much smaller than GD, also making it a less attractive simulant for sorption processes. Both DEHP and DIMP are closer in structure to GD, and DEHP appears to be the best match based on both log K_{ow} and structure.

An ideal simulant to simulate sorption of VX would have similar pK_a and log K_{ow} values; however, apart from amiton, the use of which is restricted, no VX simulants identified in the literature are ionizable. Assuming that only the neutral fraction of VX sorbs appreciably, suitable simulants for VX will be those that have a similar log K_{ow} value. The best matches are malathion, DEP, and diethyl pimelate (Table 3). Based on both structure and log K_{ow}, malathion is the best simulant to represent VX sorption. DEP contains a large aromatic group and the structure of diethyl pimelate differs considerably from that of VX. In addition, the difference between the log K_{ow} value of diethyl pimelate and VX is relatively large.

4.2 Volatilization

Volatilization of chemical agents will be governed by K_H. For HD, the closest simulant matches are: MS, DEM, diethyl adipate, DMA and diethyl pimelate (Table 1). For GA, the closest simulant matches based on K_H are DPGME, DOP, and DEEP (Table 2). For GD and GB, the closest simulant matches are (in order) ethanol, DEEP, and DEM (Table 2). For VX, the closest simulant matches are malathion and diethyl pimelate (Table 3).

4.3 Biodegradability

The biodegradability of CWAs will be governed primarily by chemical structure and to a lesser extent by aqueous solubility as typical environmental concentrations of CWAs will be well below solubility limits. The most representative simulants for HD are CEES, CEMS, diethyl pimelate, and CEPS (Figure 1). Based on structural similarity, the most representative simulants for G-agents are DMMP, DEEP, DIMP, DPCP, TMP, and DFP (Figure 2). For VX, all simulants are quite different structurally, and the most representative simulants are malathion and amiton (Figure 3).

While simulants for the assessment of CWA biodegradability were selected on the basis of structural similarity in this work, there is on-going work on structure-activity relationships (SARs) for the prediction of biodegradability [30]. Use of SARs may result in improved simulant selection in the future as this discipline continues to evolve. Most useful for CWA simulant selection would be heterologous models that provide rate constant information. Raymond et al. [30] provides a comprehensive review of homologous and heterologous structure-based biodegradation models.

4.4 Hydrolysis

The selection of appropriate simulants for hydrolysis will depend primarily on the presence of the bonds in the simulant compounds at which the hydrolysis reaction occurs in the original agent. The best simulant will closely match the structure of the original agent and can potentially form the same or similar hydrolysis product(s). For example, during GB hydrolysis, reactions occur at the P-F bond and the P-alkoxy bond to produce methylphosphonic acid [13]. GD hydrolyzes first through the loss of fluorine and then through a slower reaction, the loss of the alkoxy group [14] to form methylphosphonic acid. GA hydrolysis follows a more complex

pathway, but the ultimate hydrolysis product formed is phosphoric acid, which results from reaction at the P-N and P-CN bonds and loss of an ethyl group [13]. Because the presence of the P-F or P-CN bond is what causes the toxicity of G-agents, these bonds are not typically present in simulants. There are, however, a number of potential simulants for GA, GB and GD that have similar molecular structures including DMMP, DIMP, TEP, TMP, DEEP, and DFP. For GB and GD, DFP may be the best choice because DFP contains a P-F bond and is structurally similar to these CWAs. None of the simulants identified have the P-N bond present in GA.

HD hydrolysis occurs via a complex pathway, but the ultimate product is thiodiglycol, which is formed via a dechlorination reaction. For HD, the best simulant choices based on structural similarities are CEES (half-mustard) and CEMS as these compounds still retain one ethyl chloride functional group.

For VX, the best simulant choice is DEPPT (see Fig. 3). Hydrolysis of DEPPT in aqueous NaOH occurs with 86% P-S and 14% P-O bond breakage to produce the O-ethyl phenyl phosphonate and S-ethyl phenylphosphonate ions. VX hydrolyzes similarly with a 78/22 distribution of products from P-S and P-O bond breakage [9].

Malathion has been used to simulate VX hydrolysis [1,31]. The hydrolysis rate of malathion and the hydrolysates formed are dependent on pH and temperature. Under acidic conditions, malathion monocarboxylic acid (malathion monoacid) was found to be the only degradation product (C-O cleavage), and malathion dicarboxylic acid (malathion diacid) was expected to form at longer reaction times [32]. P-S cleavage may also occur, which leads to the formation of o,o-dimethyl phosphorothionic acid and diethyl thiosuccinate [33].

Malathion hydrolysis under alkaline conditions occurs via competing reactions. Formation of malathion monoacid (C-O cleavage) becomes increasingly important at low temperature,

while formation of diethyl fumarate, ethyl hydrogen fumarate and o,o-dimethyl phosphorodithioic acid (C-S cleavage) dominates at elevated temperatures [32]. In general, malathion hydrolysis is slowest at pH 4. At pH 5 and 7 at 20°C, the malathion hydrolysis half-life will be on the order of 10,000 h and 100 h, respectively. Based on this information, malathion could also be used to simulate VX hydrolysis, but high temperatures and/or alkaline conditions are required for malathion hydrolysis to proceed at a reasonable rate.

Finally, estimates of the half-life of potential simulants would be valuable. Unfortunately, half-life predictions using SPARC [25] did not match well with published data for CWAs so half-life predictions for simulants were not considered reliable. For example, SPARC predicted a hydrolysis half life of approximately 6000 yr for VX while measured values are 17-42 d.

5.0 Mammalian Toxicity of CWA simulants

Toxicity should also be considered in the selection of an appropriate CWA simulant. Information on the human and non-human toxicities of CWAs and many CWA simulants is presented as LD_{50} and LC_{50} values in Table 5. In general, nerve agents are the most potent chemical agents, with relative potencies: VX > GD ≈ GF> GB>GA [34]. Many CWA simulants exhibit some of the same toxicological effects as the original CWAs while other simulants are more benign. Table 5 lists the results of a qualitative comparison of simulant toxicity relative to the toxicity of the original CWA, when data for similar pathways and target animals were available. If data for similar pathways and target animals was not available, the qualitative assessment was not determined (ND).

For the G-agents, the LD_{50} value for oral exposure in rats is 1.06 mg/kg for GA [35], while values ranging from 0.10 to 1.06 mg/kg have been reported for GB via this pathway [35,36]. On

the basis of oral exposure in rats, most G-agent simulants are less toxic than the original agents. However, DFP and paraoxon have similar toxicities to GA and GB (Table 5). Exposure to BUSH may result in eye, skin, and respiratory tract irritation, muscle weakness, malaise, sweating, nausea, vomiting, headache and confusion [37,38]. DFP is a highly toxic cholinesterase inhibitor [39] and exhibits toxicity effects similar to other organophosphorus compounds. Similarly, DIMP, a by-product formed during GB synthesis, has similar anti-acetylcholinesterase activity to GB [40]. Eight-to-ten week old calves given a single dose of 1000 mg DIMP/kg exhibited ataxia followed by depression, prostration and death within two hours [41]. No toxicity data other than carcinogenicity and mutagenicity testing on rats is available for DMMP. However based on structure, human toxicity should be similar to DIMP. Exposure to paraoxon, an oxidation product of parathion, results in similar effects as exposure to organophosphorus insecticides, including headaches, blurred vision, weakness, nausea, cramps, diarrhea, and discomfort in the chest [42]. Signs include sweating, miosis, tearing, salivation and other excessive respiratory tract secretion, vomiting, and uncontrollable muscle twitches followed by muscular weakness [42]. TMP is a strong irritant to skin and eyes and is toxic by inhalation or ingestion [43]. Other G-agent simulants exhibit reduced toxicity relative to CWAs. DPGME was found to be low in toxicity by both inhalation and dermal contact [44] and although some ethyl phosphate derivatives are highly toxic cholinesterase inhibitors, TEP is thought to be only a weak enzyme inhibitor [45]. Studies indicate that ECA is a severe eye irritant [46], but more severe symptoms of ECA exposure were not identified. There is very limited data on the toxicological effects of DOP on humans. Only mild gastric disturbances were reported for two subjects [47]. The animal and ecotoxicity of DOP also appears to be low, although DOP can induce cellular transformation and has been shown to be carcinogenic in rats and mice [47].

Reported LD_{50} values for HD are 2.4 mg/kg and 8.1 to 9.7 mg/kg [48] for oral exposure in rats and mice, respectively. One common HD simulant, CEES (half-mustard), which is considered to be a blister agent, has a relatively low LD_{50} of 252 mg/kg (rat oral) (Table 5). Although toxicity data were not found for CEMS or CEPS, they, too, are assumed to have similar toxicities to HD based on structural similarity. Diethyl adipate has a relatively low toxicity, and has been reported to cause slight irritation when applied to the skin [49]. In general, adipates are thought to have similar or slightly lower toxicities than phthalate esters, although there is less data available for adipates [50]. The symptoms of MS poisoning are similar to those of aspirin poisoning [51]. Generally, ingestion of salicylates at doses larger than 150 mg/kg can produce toxic symptoms such as tinnitus, nausea, and vomiting. Serious toxicity can be observed with ingestions greater than 400 mg/kg, with severe vomiting, hyperventilation, hyperthermia, confusion, coma, and convulsions [52].

LD_{50} values reported for VX include 0.077 to 0.128 mg/kg and 0.007 to 0.010 mg/kg for oral and iv exposure in rats, respectively [35,53]. In general, the V-agent simulants identified in this study are less toxic than VX, but amiton, malathion, and parathion are still very toxic organophosphorus insecticides with anticholinesterase activity. These compounds can be toxic by ingestion, inhalation, or dermal contact. DEP and DES exhibit little acute or chronic toxicity, but they do not closely mimic VX properties [49,54].

LD_{50} values reported for lewisite include 50 mg/kg for oral exposure in rats and 15 mg/kg for percutaneous exposure for dogs [54]. No toxicity data could be identified for lewisite oxide, but the LD_{50} values for phenylarsine oxide result in a high toxicity classification for this simulant (Table 5) [55].

In summary, the identified simulants represent a range of toxicities. While the simulants exhibit decreased toxicity relative to the original agents, some are still quite toxic and some are assumed to be nearly as toxic (e.g., CEES, DFP, paraoxon) or even more toxic (e.g., phenylarsine oxide) as the original agents. All simulant compounds were found to be available from commercial suppliers, with the exception of DEPPT.

6.0 Conclusions

A summary of the most favorable simulant choices for each CWA as a function of the environmental fate process to be evaluated is presented in Table 6. For most of the agents reviewed (HD, G-agents, VX), a number of simulants may be appropriate while only one simulant was identified for lewisite oxide. No single simulant is best for all environmental fate processes considered, therefore, a number of simulants are required to represent CWAs in experiments to fully characterize fate and transport.

Ideally, it would be possible to perform a quantitative analysis of tradeoffs between alternative simulants, their relatedness to a CWA for a specific fate process, and toxicity. In reality, these factors will be considered qualitatively along with the available laboratory facility, research objectives and compound availability. Emphasis should be on selection of the lowest toxicity simulant that adequately represents the fate process(es) of interest. In future work, our objective is to develop and validate a model to simulate the fate and transport of CWAs during refuse decomposition. To meet this objective, the use of malathion is appropriate because (1) its behavior will be impacted by hydrolysis, biodegradation, and sorption/desorption, and (2) it is available in radiolabeled form which facilitates measurement in a complex environmental matrix. Once a model is validated using malathion, it can be used to simulate the fate and transport of actual CWAs using published physical-chemical property data although biodegradability will

remain more uncertain. For model validation, a chemical that undergoes all potential fate processes is more important than its suitability as a simulant for a specific CWA.

Acknowledgements

This research was supported by the US EPA through the Safe Buildings Program, Susan Thorneloe, Senior Project Officer. The input of Susan Thorneloe and Paul Lemieux of the US EPA is acknowledged.

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Table 1. Physical-Chemical Properties of HD and Potential Surrogates[a].

Compound	Abbreviation	Formula	CAS no.	MW (g/mol)	mp (°C)	bp (°C)	vp (mm Hg)	log K_{ow}	solubility (mg/L)	K_H (at 25°C)	hydrolysis $t_{1/2}$ (min)	pK_a
distilled mustard	HD	$C_4H_8Cl_2S$	505-60-2	159.07	14.45	218	0.11	2.41-2.55	684 (25°C)	9.8×10^{-4}	8.5 (25°C, DI water)	-
2-chloroethyl ethyl sulfide	CEES/HM	C_4H_9ClS	693-07-2	124.63	-48.6[b]	156.5	3.4	2.2[d]	1062[b] (25°C)	$1.5\times10^{-2(d)}$		-
diethyl adipate		$C_{10}H_{18}O_4$	141-28-6	202.25	-19.8	245	5.77×10^{-2}	2.66[d]	4230 (20°C)	$1.1\times10^{-4\,(d)}$		-
diethyl malonate	DEM	$C_7H_{12}O_4$	105-53-3	160.17	-50	200	0.27	0.96	2.32×10^{4} (37°C)	$9.5\times10^{-5(d)}$		-
diethyl pimelate		$C_{11}H_{20}O_4$	2050-20-6	216.28	-24	254	3.10×10^{-3}	3.07[d]	1970 (25°C)	1.8×10^{-5}		-
dimethyl adipate	DMA	$C_8H_{14}O_4$	627-93-0	174.20	10.3	115[c]	6.0×10^{-2}	1.03	6000 (25°C)	$6.7\times10^{-5(d)}$		-
methyl salicylate	MS	$C_8H_8O_3$	119-36-8	152.15	-8	223	0.04	2.55	700 (30°C)	4.0×10^{-3}		0.213[d]
2-chloroethyl methyl sulfide	CEMS	C_3H_7ClS	542-81-4	110.6	-61[b]	132[b]	8.98[b]	1.62[d]	3245[b] (25°C)	$7.6\times10^{-3(d)}$		-
chloroethyl phenyl sulfide	CEPS	C_8H_9ClS	5535-49-9	172.67	17[b]	257[b]	$1.86\times10^{-2(b)}$	3.58[d]	84[b] (25°C)	$3.0\times10^{-3(d)}$		-

[a]Data sources include [10,14,16,19,29,56].
[b]Estimated with EPISuite v.3.12 [29].
[c]at 13 mm Hg.
[d]Predicted using SPARC [25].
MW is molecular weight; mp is melting point; bp is boiling point; vp is vapor pressure; K_H is the dimensionless Henry's law constant.

Table 2. Physical-Chemical Properties of G-agents and Potential Surrogates[a].

Compound	Abbreviation	Formula	CAS no.	MW (g/mol)	mp (°C)	bp (°C)	vp (mm Hg)	log K_{ow}	solubility (mg/L)	hydrolysis $t_{1/2}$ (min)	K_H (at 25°C)	pK_a
Tabun	GA	$C_5H_{11}N_2O_2P$	77-81-6	162.13	-50[b]	248	0.057	0.394	7.2×10^4 (20°C)	840-1680 (25°C, neutral pH)	6.5×10^{-7}[(b)]	-
Sarin	GB	$C_4H_{10}FO_2P$	107-44-8	140.1	-56	158	2.1	0.3	1.0×10^6 (25°C)	2340 (25°C, pH 7.5)	3.8×10^{-4}	-
Soman	GD	$C_7H_{16}FO_2P$	96-64-0	182.17	-42	198	0.4	1.78	2.1×10^4 (25°C)	3600 (25°C, pH 6)	1.9×10^{-4}	-
1-butanethiol	BUSH	$C_4H_{10}S$	109-79-5	90.19	-115.7	98.5	45.5	2.28	597 (20°C)		3.7×10^{-1}	0.15[c]
bis (2-ethylhexyl) phthalate	DOP	$C_{24}H_{38}O_4$	117-81-7	390.6	-55	384	1.42×10^{-7}	7.6	0.27 (25°C)		1.1×10^{-5}	-
diethyl ester phosphonic acid	DEHP	$C_4H_{11}O_3P$	762-04-9	138.1	<25	138	11.2	3.01[c]	1.0×10^{6}[(b)] (25°C)		7.4×10^{-2}[(c)]	-
diethyl malonate	DEM	$C_7H_{12}O_4$	105-53-3	160.17	-50	200	0.27	0.96	2.32×10^4 (37°C)		9.5×10^{-5}[(c)]	-
diisopropyl fluorophosphate	DFP	$C_6H_{14}FO_3P$	55-91-4	184.15	-82	183	0.58	4.3[c]	1.54×10^4 (25°C)		5.3[(c)]	-
diisopropyl methylphosphonate	DIMP	$C_7H_{17}O_3P$	1445-75-6	180.19	<25	121[d]	0.277	1.03	1500 (25°C)		1.80×10^{-3}	-
dimethyl methylphosphonate	DMMP	$C_3H_9O_3P$	756-79-6	124.08	-48[b]	181	0.96	-0.61	1×10^6 (25°C)		5.3×10^{-5}	-
dipropylene glycol monomethyl ether	DPGME	$C_7H_{16}O_3$	34590-94-8	148.2	-15.5 [b]	188.3	0.55	-0.35 [b]	1×10^6 (25°C)		4.7×10^{-8}[(b)]	-
Ethanol		C_2H_6O	64-17-5	46.07	-114.1	78.2	59.3	-0.31	1×10^6		2.1×10^{-4}	-
ethyl chloroacetate	ECA	$C_4H_7ClO_2$	105-39-5	122.55	-21	144.3	4.87	0.94	1.94×10^4 (30°C)		1.7×10^{-3}	-
diethyl 4-nitrophenyl phosphate	paraoxon	$C_{10}H_{14}NO_6P$	311-45-5	275.20	300	375[b]	1.10×10^{-6}	1.98	3640 (20°C)		1.5×10^{-3}[(c)]	-

Table 2. Physical-Chemical Properties of G-agents and Potential Surrogates (cont.)

Compound	Abbreviation	Formula	CAS no.	MW (g/mol)	mp (°C)	bp (°C)	vp (mm Hg)	log K_{ow}	solubility (mg/L)	hydrolysis $t_{1/2}$ (min)	K_H (at 25°C)	pK_a
triethyl phosphate	TEP	$C_6H_{15}O_4P$	78-40-0	182.16	-56	215	0.39	0.8	5×10^5 (25°C)		6.1×10^{-5}	-
trimethyl phosphate	TMP	$C_3H_9O_4P$	512-56-1	140.08	-46	197.2	0.85	-0.65	5×10^5 (25°C)		2.9×10^{-7}	-
diethyl ethyl phosphonate	DEEP	$C_6H_{15}O_3P$	78-38-6	166.16	-13[b]	198	0.315	0.66	1750 (25°C)		1.2×10^{-4}	-
Diphenyl chlorophosphate	DPCP	$C_{12}H_{10}ClO_3P$	2524-64-3	268.64	362[b]	86.5[b]	1.7×10^{-5}[(b)]	5.95[c]	-		1.1×10^{-2}[(c)]	-

[a] Data compiled from the following sources [14,16,19,29,56,57].
[b] Estimated with EPISuite v.3.12 [29].
[c] Predicted using SPARC [25].
[d] at 10 mm Hg
MW is molecular weight; mp is melting point; bp is boiling point; vp is vapor pressure; K_H is the dimensionless Henry's law constant

Table 3. Physical-Chemical Properties of VX and Potential Surrogates[a].

Compound	Abbreviation/ Common Name	Formula	CAS no.	MW (g/mol)	mp (°C)	bp (°C)	vp (mm Hg)	log K_{ow}	solubility (mg/L)	K_H at 25°C	hydrolysis $t_{1/2}$ (min)	pK_a
VX		$C_{11}H_{26}NO_2PS$	50782-69-9	267.37	<-51	292	7×10^{-4}	2.09	3×10^{4} (25°C)	1.43×10^{-7}	24,480-60480 (25°C, pH 7)	~9[b]
bis (2-ethyl-1-hexyl) 2-ethyl-1-hexyl phosphonate		$C_{24}H_{51}O_3P$	126-63-6	418.65	85.8[c]	434.3[c]	3.15×10^{-7}[(c)]	11.98[(d)]	1.8×10^{-5}[(c)] (25°C)	3.1×10^{-1}[(d)]		-
bis (2-ethylhexyl) phosphonate	BIS	$C_{16}H_{35}O_3P$	3658-48-8	306.43	75.9[c]	349.5[c]	4.47×10^{-5}[(c)]	8.26[(d)]	3.4[c] (25°C)	6.1×10^{-1}[(d)]		-
diethyl malonate	DEM	$C_7H_{12}O_4$	105-53-3	160.17	-50	200	0.27	0.96	2.32×10^{4} (37°C)	9.5×10^{-5}[(d)]		-
diethyl phthalate	DEP	$C_{12}H_{14}O_4$	84-66-2	222.24	-40.5	295	2.10×10^{-3}	2.42	1,080 (25°C)	2.5×10^{-5}		-
diethyl pimelate		$C_{11}H_{20}O_4$	2050-20-6	216.28	-24	254	3.10×10^{-3}	3.07[(d)]	1,970 (25°C)	1.8×10^{-5}		-
diethyl sebacate	DES	$C_{14}H_{26}O_4$	110-40-7	258.36	5	305	5.08×10^{-4}	4.36[(d)]	80 (20°C)	1.5×10^{-4}[(d)]		-
S-[1,2-bis(ethoxycarbonyl) ethyl] o,o-dimethyl phosphorodithioate	malathion	$C_{10}H_{19}O_6PS_2$	121-75-5	330.36	2.8	156[e]	3.38×10^{-6}	2.36	143 (20°C)	2.0×10^{-7}		-
o,o-diethyl-o-p-nitrophenyl thiophosphate	parathion	$C_{10}H_{14}NO_5PS$	56-38-2	291.26	6.1	375	6.68×10^{-6}	3.83	11 (20°C)	1.2×10^{-5}		-
o,o-diethyl s-[2-(diethylamino)ethyl] phosphorothiolate	amiton	$C_{10}H_{24}NO_3PS$	78-53-5	269.34	<25	110[f]	2.67×10^{-4}[(c)]	3.94[(d)]	4.67×10^{4}[(c)]	1.15×10^{-8}		8.6[g]
o,s-diethyl phenyl-phosphonothioate	DEPPT	$C_{10}H_{15}O_2PS$	57557-80-9	230.26		98-100	9.03×10^{-4}[(h)]	4.29[(d)]	1,400[(h)]			-

[a] Data sources include [10,14,16,19,29,56,58].
[b] Reported pK_a values for VX range from 8.6 – 9.12 [23,24].
[c] Estimated with EPISuite v.3.12 [29].
[d] Predicted using SPARC [25].
[e] at 0.7 mm Hg
[f] at 0.2 mm Hg
[g] Predicted using ChemSilico software [59]
[h] Estimated values from SciFinder Scholar [58]
MW is molecular weight; mp is melting point; bp is boiling point; vp is vapor pressure; K_H is the dimensionless Henry's law constant.

Table 4. Physical and Chemical Properties of Lewisite, Lewisite Oxide and Phenylarsine Oxide[a].

Compound	Abbreviation	Formula	CAS no.	MW (g/mol)	mp (°C)	bp (°C)	vp (mm Hg)	log K_{ow}	solubility (mg/L)	K_H at 25°C	hydrolysis $t_{1/2}$ (min)	pK_a
lewisite	L	$C_2H_2AsCl_3$	541-25-3	207.32	-1.2	196	0.58	2.56	500[b]	$1.1\times10^{-2(c)}$	0.7	-
lewisite oxide		C_2H_2AsClO	3088-37-7	152.41	18[c]	120.5[c]	15.3[c]	1.94[c]	13072[c] (25°C)	$7.7\times10^{-2(c)}$		-
phenylarsine oxide		C_6H_5AsO	637-03-6	168.03	145	195[c]	$2.54\times10^{-2(c)}$	2.44[c]	1800[c]	$4.5\times10^{-4(c)}$		-

[a]Data sources include [14,17,29].
[b]Temperature not reported
[c]Estimated with EPISuite v.3.12 [29].
MW is molecular weight; mp is melting point; bp is boiling point; vp is vapor pressure; K_H is the dimensionless Henry's law constant

Table 5. Available LD_{50} and LC_{50} values for CWAs and CWA simulants.

CWA	CWA Toxicity LD_{50} or LC_{50} [1]	Simulant	LD_{50} or LC_{50} (Mouse Oral)	LD_{50} or LC_{50} (Rat Oral)	LD_{50} or LC_{50} (other data)[1]	Toxicity Relative to Original CWA[2]
G-agents	**GA** Mouse oral 0.287 mg/kg (36); Rat oral 1.06 mg/kg (35); Rat iv 0.07 mg/kg (35); Mouse iv 0.31 mg/kg (35) **GB** Human oral 28 mg/kg (60); Rat oral 0.55 mg/kg (36), 0.10 mg/kg (35), 0.87-1.06 mg/kg (36); Rat iv 0.045 mg/kg (35); Mouse iv 0.07 – 0.113 mg/kg (35) **GD** Rat iv 0.045 mg/kg (36); Rat ip 0.098 mg/kg (36); Dog sc 0.012 mg/kg (36)	BUSH	3,000 mg/kg (38)	1,500 mg/kg (60)		low
		DOP	>30,000 mg/kg (60)	>25,000 mg/kg (60)	Rabbit oral 33,900 mg/kg; Guinea pig oral 26,300 mg/kg; Guinea pig dermal 10,000 mg/kg; Rabbit dermal 25,000 mg/kg (60)	low
		DEHP		3,900 mg/kg (55)		low
		DEM	6,400 mg/kg (55)	~15,700 mg/kg (55)		low
		DFP	2 mg/kg (55)	5 mg/kg (60)		equivalent
		DIMP		826 mg/kg (60)	Female mink oral 503 mg/kg; Male New Zealand rabbit dermal 1,100 mg/kg (60,61)	low
		DMMP	>6,810 mg/kg (55)	8,210 mg/kg (55)		low
		DPGME		5,350 mg/kg (62)	Rabbit dermal 9,500 mg/kg (62)	low
		ethanol	3,450 mg/kg (39)	7,060 mg/kg (60)	Guinea pig oral 5,600 mg/kg; Dog oral 5,500 mg/kg (39,60)	low
		ECA		180 mg/kg (55)	Rabbit skin 230 mg/kg (60)	low
		paraoxon	0.76 mg/kg (60)	1.8 mg/kg (60)		equivalent
		TEP	1,180 mg/kg (55)		Rat ip 800 mg/kg (76)	low
		TMP	1,470 mg/kg (55)	840 mg/kg (55)		low
		DEEP	2500 mg/kg (55)	2330 mg/kg (55)		low
		DPCP				ND[3]

Table 5. Available LD_{50} and LC_{50} values for CWAs and CWA simulants (contd.)

CWA	CWA Toxicity LD_{50} or LC_{50}	Simulant	LD_{50} or LC_{50} (Mouse Oral)	LD_{50} or LC_{50} (Rat Oral)	LD_{50} or LC_{50} (other data)	Toxicity Relative to Original CWA
HD	Rat oral 2.4 mg/kg (48); Rat sc 3.4 mg/kg (48); Mouse oral 8.1-9.7 mg/kg (48); Mouse sc 19.3 mg/kg (63); Mouse ip 4.8 mg/kg (63)	CEES/HM		252 mg/kg (55)	Mouse sc 566 mg/kg (63); Mouse ip 17.7 mg/kg (63)	low/equiv.
		diethyl adipate		>1,600 mg/kg (49)		low
		DEM	6,400 mg/kg (55)	~15,700 mg/kg (55)		low
		diethyl pimelate				ND
		DMA			Rat ip ~1,900 mg/kg (55)	low
		MS	1,110 mg/kg (55)	887 mg/kg (49)	Adult oral 500 mg/kg; Rabbit oral 2,800 mg/kg; Guinea pig oral 1,060 mg/kg; Dog oral 2,100 mg/kg (49)	low
		CEMS				ND
		CEPS				ND
VX	Rat oral 0.077-0.128 mg/kg (53); Rat iv 0.007 – 0.010 (35, 53); Mouse iv 0.012-0.015 mg/kg (53); Rabbit sc 0.015 mg/kg (53)	diethyl pimelate				ND
		malathion	190 mg/kg (60)	290 mg/kg (65)	Mouse skin 2,330 mg/kg; Rabbit oral 250 mg/kg; Rabbit skin 4,100 mg/kg (60)	low
		parathion	5 mg/kg (60)	2 mg/kg (60)	Human oral 3 mg/kg; Rat skin 6.8 mg/kg (60)	low (but very toxic)
		amiton		3.3 mg/kg		low (but very toxic)
		DEPPT				ND
Lewisite	Rat oral 50 mg/kg; Dog percutaneous 15 mg/kg (54)	phenylarsine oxide			Mouse ip 1.93 mg/kg (55); Rabbit iv 0.79 mg/kg (55)	high

[1] iv = intraveneous, sc = subcutaneous, ip = intraperitoneal

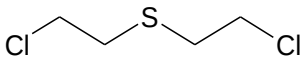
[2] Qualitative toxicity assessment determined by comparison of available LD_{50} values for simulant and original CWA for a given exposure pathway and target organism. Simulant toxicity data within one order of magnitude when compared to the original CWA were determined to have 'equivalent' toxicity.

[3] Not determined because no LD_{50} values were available for the simulant.

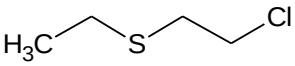
Table 6. Summary of most favorable surrogates for select environmental fate processes.

Experiment	HD	GA	GB	GD	VX
Adsorption/ Desorption	CEES CEMS (nd) MS*	DEEP* TEP (nd) ECA		DEHP*	malathion*
Volatilization	MS DEM* diethyl adipate DMA (nd) diethyl pimelate (nd)	DPGME DOP* DEEP	ethanol DEEP DEM*		malathion* diethyl pimelate (nd)
Biodegradability	CEES* CEMS (nd) diethyl pimelate (nd) CEPS (nd)	DMMP* DEEP DIMP DPCP (nd) TMP DFP			malathion* amiton
Hydrolysis	CEES* CEMS (nd)	DMMP* DIMP TEP (nd) TMP DEEP DFP			DEPPT (nd) malathion*

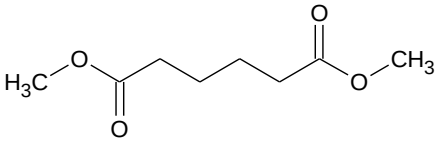
* denotes lowest toxicity simulant based on rat oral data presented in Table 5.
nd – no rat oral toxicity data



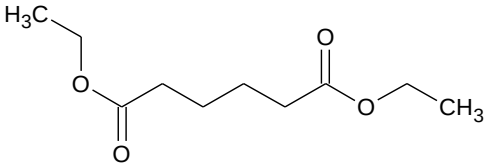
Mustard gas



CEES/HM



dimethyl adipate



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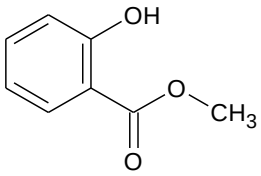

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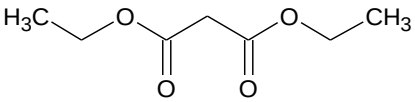

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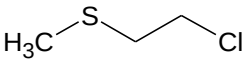

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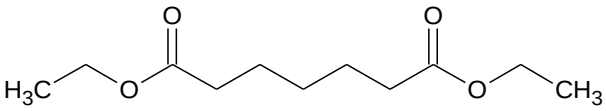

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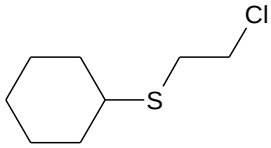
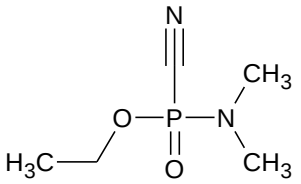


CEPS

Figure 1. Molecular structures of HD and HD surrogates.



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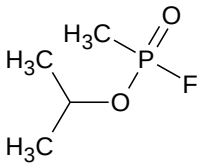

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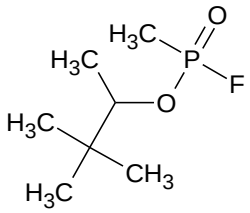

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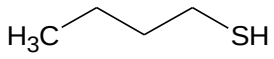

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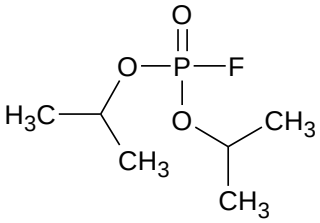

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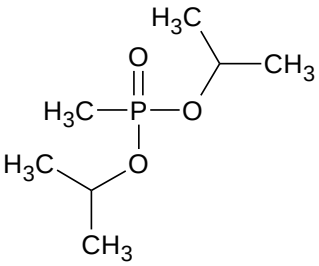

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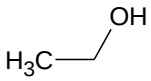
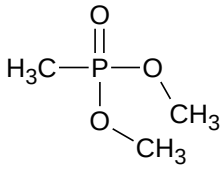


ethanol



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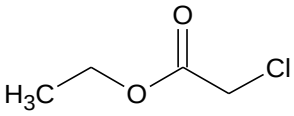

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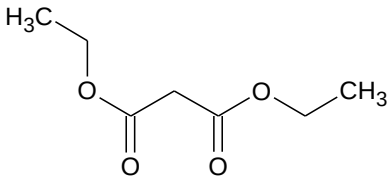

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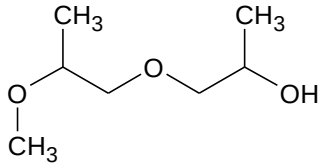

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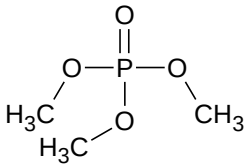

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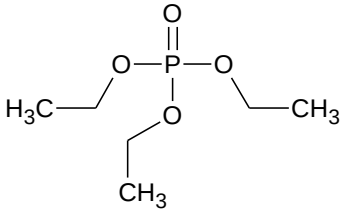

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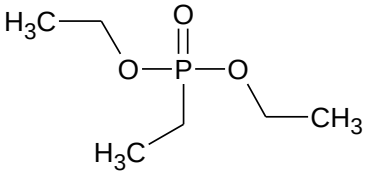

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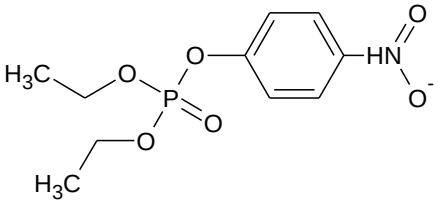
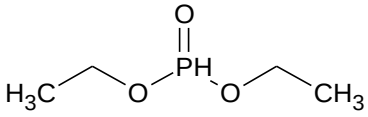


paraoxon



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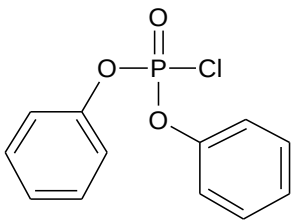

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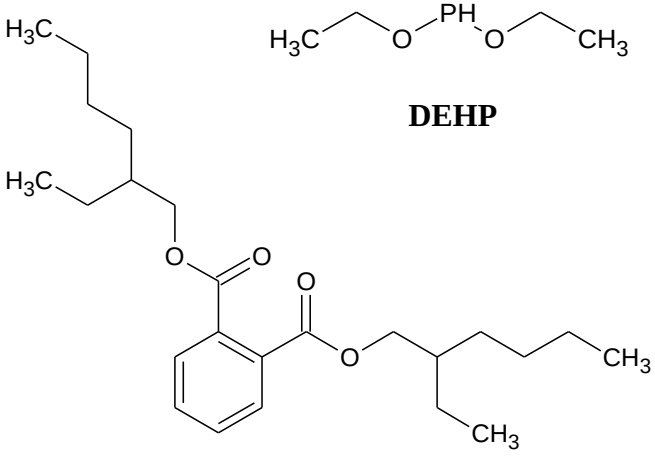
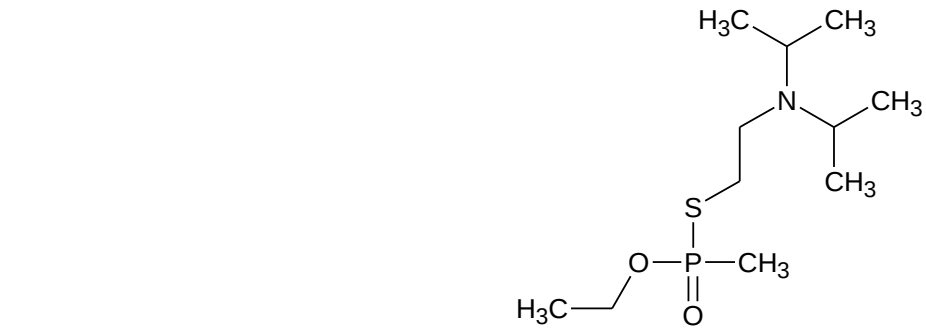
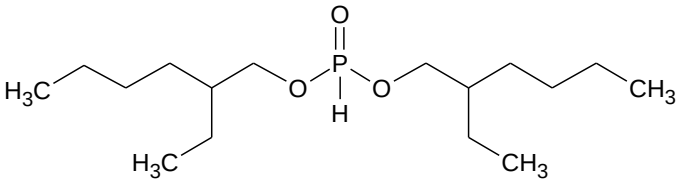


DOP

Figure 2. Molecular structures of GA, GB, GD and G-agent surrogates



VX



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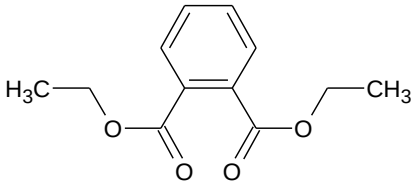

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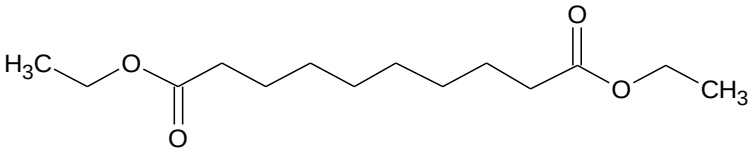

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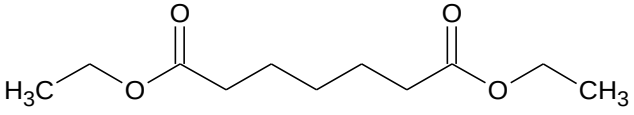

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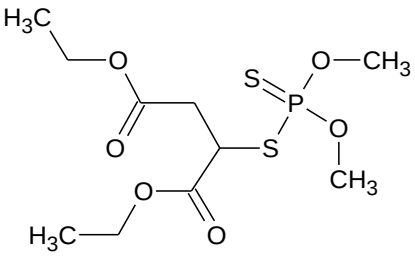
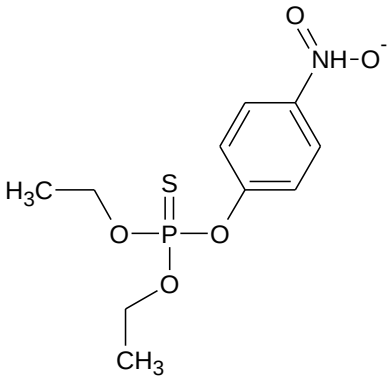
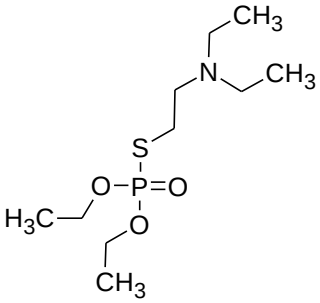


malathion



parathion



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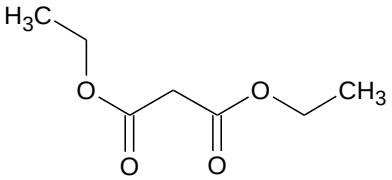

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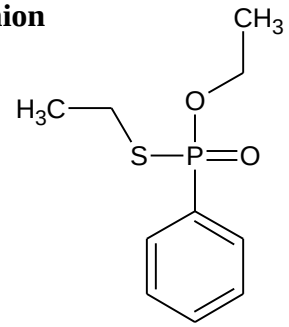

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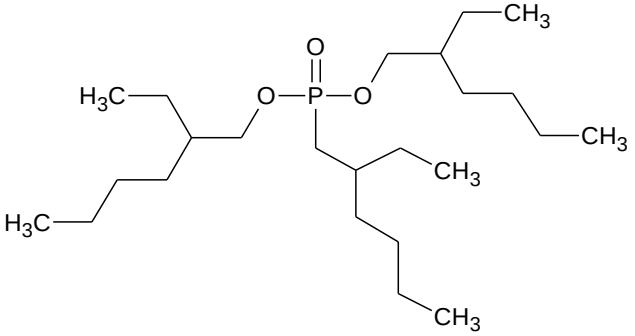
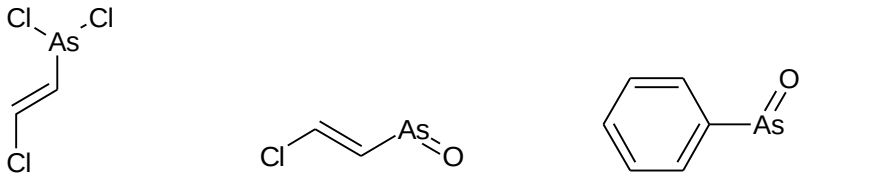


bis (2-ethyl-1-hexyl) 2-ethyl-1-hexyl phosphonate

Figure 3. Molecular structures of VX and VX surrogates.



Lewisite **lewisite oxide** **phenylarsine oxide**

Figure 4. Molecular structures of lewisite, lewisite oxide and phenylarsine oxide.