The Sources, Fate, and Toxicity of Chemical Warfare Agent Degradation Products

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We include in this review an assessment of the formation, environmental fate, and mammalian and ecotoxicity of CW agent degradation products relevant to environmental and occupational health. These parent CW agents include several vesicants: sulfur mustards [undistilled sulfur mustard (H), sulfur mustard (HD), and an HD/agent T mixture (HT)]; nitrogen mustards [ethylbis(2-chloroethyl)amine (HN1), methylbis(2-chloroethyl)amine (HN2), tris(2-chloroethyl)amine (HN3)], and Lewisite; four nerve agents {*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX), tabun (GA), sarin (GB), and soman (GD)}; and the blood agent cyanogen chloride. The degradation processes considered here include hydrolysis, microbial degradation, oxidation, and photolysis. We also briefly address decontamination but not combustion processes. Because CW agents are generally not considered very persistent, certain degradation products of significant persistence, even those that are not particularly toxic, may indicate previous CW agent presence or that degradation has occurred. Of those products for which there are data on both environmental fate and toxicity, only a few are both environmentally persistent and highly toxic. Major degradation products estimated to be of significant persistence (weeks to years) include thiodiglycol for HD; Lewisite oxide for Lewisite; and ethyl methyl phosphonic acid, methyl phosphonic acid, and possibly *S*-(2-diisopropylaminoethyl) methylphosphonothioic acid (EA 2192) for VX. Methyl phosphonic acid is also the ultimate hydrolysis product of both GB and GD. The GB product, isopropyl methylphosphonic acid, and a closely related contaminant of GB, diisopropyl methylphosphonate, are also persistent. Of all of these compounds, only Lewisite oxide and EA 2192 possess high mammalian toxicity. Unlike other CW agents, sulfur mustard agents (e.g., HD) are somewhat persistent; therefore, sites or conditions involving potential HD contamination should include an evaluation of both the agent and thiodiglycol. *Key words*: anticholinesterase, blood agent, CK, cyanogen chloride, decontamination, GA, GB, GD, HD, HN, hydrolysis, Lewisite, microbial degradation, nerve agent, nitrogen mustard, oxidation, sarin, soman, sulfur mustard, tabun, VX, vesicant. *Environ Health Perspect* 107:933–974 (1999). [Online 3 November 1999]
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In this review we address health issues related to chemical warfare (CW) agent disposal and stockpile destruction. Munro et al. (*1*) detailed the acute and chronic toxicity of the nerve agents tabun (ethyl *N,N*-dimethylphosphoroamidocyanidate; GA), sarin (isopropyl methylphosphonofluoridate; GB), and *O*-ethyl *S*-[2-(diisopropylamino)ethyl]methylphosphonothioate (VX). Earlier, Watson and Griffin (*2*) reviewed the acute and chronic toxicity of the vesicant agents with special emphasis on mustard carcinogenicity, and Munro et al. (*3*) evaluated nerve and blister agent antidote use, toxicity, and decontamination procedures in the context of civilian application.

During this era of CW agent demilitarization and cleanup of sites and facilities associated with chemical agent production, testing, and storage, information on the properties and toxicity of CW agent degradation products is important for risk management in site operations and restorations. Although a variety of breakdown products and impurities have previously been documented, the significance to environmental and/or occupational health has not been established.

In this review we assemble the scattered and often fragmentary literature on environmental fate of the CW agents as well as what is presently known about the potential health effects and ecotoxicity of each agent's degradation products and contaminants. We have eliminated certain compounds from potential concern and focused attention on those with known significant environmental persistence and toxicity. With the exception of the sulfur mustards, most of the CW agents are not persistent in the environment because they are subject to a variety of abiotic and biotic degradation mechanisms. It is important to identify persistent and/or toxic chemical agent breakdown products to assist in cleanup processes and to ensure worker and public safety. We generally use "environmental persistence" to refer to the presence of compounds in soil; environmental persistence is moderate for compounds that may be stable for weeks to months and high for compounds that are stable for months to years. "Persistent compounds" are characterized by low vapor pressure, low water solubility, and low rates of natural abiotic and biologic degradation. Examples include polychlorinated biphenyls and dioxins; these compounds are not related to CW agents. However, compounds with moderate-to-high water solubility that are not readily degradable or subject to hydrolysis may persist in dry soil and/or leach into groundwater, where they persist for long periods.

Toxicity depends on the route of exposure. Relevant routes of exposure for CW agent breakdown products are oral, inhalation, and dermal. Compounds that are lethal to 50% of tested animals [median lethal dose (LD_{50}) or median lethal concentration

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(LC_{50})] at < 50 mg/kg, < 50 mg/m^3, and < 200 mg/kg after single exposures are considered highly acutely toxic by the oral, inhalation, and dermal routes, respectively (*4*). Compounds with LD_{50} or LC_{50} values of 50–500 mg/kg, 50–500 mg/m^3, and 200–500 mg/kg for the respective routes are considered moderately toxic, and compounds with values higher than these ranges are considered to be of a low order of toxicity. Toxic values for chronic exposures by the respective categories and routes of exposure are generally an order of magnitude lower. For aquatic organisms, LC_{50} values of < 1 mg/L and < 0.1 mg/L are considered highly acutely and chronically toxic, respectively.

The primary warfare agents of concern within the U.S. CW agent inventory include several vesicant or blister agents: sulfur mustards {undistilled sulfur mustard (H), sulfur mustard (HD), and an HD/agent T mixture (HT)}; nitrogen mustards [ethylbis(2-chloroethyl)amine (HN1), methylbis(2-chloroethyl)amine (HN2), tris(2-chloroethyl)amine (HN3)], and the organic arsenical Lewisite]; four nerve agents [VX, GA, GB, and soman (pinacolyl methylphosphonofluoridate; GD)], and the blood agent cyanogen chloride (CK) [Table 1 (*2,5–20*)]. The nitrogen mustards, GD nerve agent, and CK were not stockpiled as part of the U.S. chemical weapons inventory, and Lewisite and GA were produced in limited quantities in the United States. The emphasis in this review is on those potential degradation products resulting from agent contact with soil or water, especially from buried chemical weapons and wastes. The principal degradation processes include photolysis, hydrolysis, oxidation, and microbial degradation. Volatilization is an important mechanism for the transfer of some CW agents from soil and water to air. Decontamination procedures may incorporate some or all of these processes. We do not discuss combustion.

We assessed each of these processes/sources of degradation products to assist those responsible for disposal, cleanup, and destruction operations to anticipate possible hazards. For example, knowledge of the environmental fate of CW agents would aid in choices of measures needed to ensure the safety of workers involved in hazardous waste cleanup and to ensure adequate remediation. It would also assist in determining the extent of possible contamination where agent wastes or munitions have been buried.

Different operations and conditions involve these various processes and therefore potentially have different breakdown products associated with a given CW agent. In general, however, photolysis is relevant in the case of spills, particularly to soil surfaces and surface waters, as well as in the event of airborne release of an agent. Hydrolysis is pertinent to warfare agents buried in moist soil, to disposal in bodies of water, or to inadvertent releases or spills into surface water bodies. Compared to many other environmental contaminants, these agents and some of their degradation products are susceptible to hydrolysis, which minimizes their transport to groundwater. Hydrolysis is also a relevant disposal option for VX stored in ton containers (alkaline hydrolysis or neutralization followed by supercritical water oxidation) (*21,22*) and is an alternate disposal option for HD stored in ton containers (hot water neutralization followed by biodegradation of the hydrolysate) (*21,23,24*). Oxidation is

Table 1. Identity and chemical and physical properties of chemical warfare agents.

Property/ parameter	Agent										
	H/HD	HT	HN1	HN2	HN3	Lewisite	VX	GA	GB	GD	CK
Chemical formula	$C_4H_8Cl_2S$	$C_4H_8Cl_2S$ $C_8H_{16}Cl_2OS_2$	$C_6H_{13}Cl_2N$	$C_5H_{11}Cl_2N$	$C_6H_{12}Cl_3N$	$C_2H_2AsCl_3$	$C_{11}H_{26}NO_2PS$	$C_5H_{11}N_2O_2P$	$C_4H_{10}FO_2P$	$C_7H_{16}FO_2P$	CNCl
CAS no.	505-60-2	63918-89-8	538-07-8	51-75-2	555-77-1	541-25-3	50782-69-9	77-81-6	107-44-8	96-64-0	506-77-4
Molecular weight	159.08	ND	170.08	156.07	205.54	207.35	267.4	162.1	140.1	182.2	61.48
Physical state	Oily liquid	Oily liquid	Liquid	Liquid	Liquid	Liquid	Oily liquid	Oily liquid	Liquid	Liquid	Volatile liquid
Color	Clear/pale yellow, black if impure	Amber/dark brown	Colorless/ pale yellow	Colorless/ pale yellow	Colorless/ pale yellow when fresh	Colorless (pure), amber/ brown (aged)	Light amber/ amber	Colorless to brown	Colorless	Colorless	Colorless
Melting point	13–14°C	1°C	-34°C	-60°C	-3.7°C	-18°C	-39°C (calculated)	-50°C	-56°C	-42°C	-6.9°C
Boiling point	215–217°C	> 228°C	Decomposes	75°C	230–235°C, decomposes	190°C	298°C, decomposes	220–246°C	158°C	198°C	12.8°C
Density, liquid (g/mL)	1.27 at 20°C	1.27 at 20°C	1.09 at 25°C	1.12	1.24	1.89 at 20°C	1.008 at 20°C	1.073 at 25°C	1.102 at 20°C	1.022 at 25°C	1.18
Vapor pressure (mmHg 20 or 25°C)	0.11	0.10	0.25	0.427	0.011	0.58	0.0007	0.037 at 20°C 0.07 at 25°C	2.10 at 20°C	0.40 at 25°C	1,000 at 25°C
Volatility (mg/m^3)	920	831	2.29	3.6	0.12	4,480	10.5	610	22,000	3,900	6,132,000
Vapor density (air = 1)	5.5	6.9	5.9	5.4	7.1	7.1	9.2	5.6	4.9	6.3	2.1
Water solubility (g/L)	0.92	Practically insoluble	12	Sparingly soluble	0.16	0.5	30	98 at 25°C	Miscible	21 at 20%	Slightly soluble
Hydrolysis rate (half-life)	8.5 min at 25°C/distilled water[a]	ND	12.5 days at 5°C	11 hr at 25°C	ND	ND, rapid hydrolysis	1,000 hr (pH 7) (pH 6)	8.5 hr (pH 7)	39 hr (pH 7) 125 hr	45 hr (pH 6.6)	5.25 hr at 20°C (pH 8.6)
Henry's Law constant (H, atm × m^3/mol)[b]	2.1×10^{-5}	ND	ND	8.5×10^{-8}	3×10^{-7}	3.2×10^{-4}	3.5×10^{-9}	1.52×10^{-7}	5.4×10^{-7}	4.6×10^{-6}	ND
Log K_{ow}	1.37	ND	ND	0.9	ND	ND	2.09	0.384	0.299	1.824	ND
Log K_{oc}	2.12	ND	ND	1.86	2.83	ND	2.5	2.02	1.77	1.17	ND

Abbreviations: CK, cyanogen chloride; GA, ethyl *N,N*-dimethylphosphoroamidocyanidate (tabun); GB, isopropyl methylphosphonofluoridate (sarin); GD, pinacolyl methylphosphonofluoridate (soman); H/HD, bis(2-chloroethyl)sulfide; HN1, ethylbis(2-chloroethyl)amine; HN2, methylbis(2-chloroethyl)amine; HN3, tris(2-chloroethyl)amine; HT, 60% bis(2-chloroethyl)sulfide (agent HD) + 40% bis[2-(2-chloroethylthio)ethyl] ether (agent T); Log K_{oc}, log organic carbon partition coefficient, an estimate of the tendency of a chemical to adsorb to the organic carbon phase in soil or sediment; Log K_{ow}, log octanol/water partition coefficient, an estimate of a chemical's tendency to bioaccumulate in organisms; ND, no data; VX, *O*-ethyl-*S*-[2-(diisopropylamino)ethyl]methylphosphonothioate. Data from Watson and Griffin (*2*), Rosenblatt et al. (*5*), Forsman et al. (*6*), Franke (*7*), Small (*8*), Clark (*9*), Goldman and Dacre (*10*), U.S. Army (*11*), Trochimowicz (*12*), Rosenblatt et al. (*13*), Budavari et al. (*14*), USACHPPM (*15*), HSDB (*16–18*), Opresko et al. (*19*), and Major (*20*).

[a]Hydrolysis limited by rate of solution. [b]Values for L, GA, and GB calculated from $H = H^* \times RT$ where H^* = ratio of the volatility and solubility (in milligrams per cubic meter), R = gas constant (8.2×10^{-5} atm × m^3/mol × degrees Kelvin), and T = temperature in Kelvin (293.15 K).

relevant to compounds in contact with air or natural oxidants in soil or water, and also for decontamination systems (oxidative detoxification). Microbial degradation is of interest in cases of burial or spills on soil and the hot water neutralization/biodegradation of hydrolysate option for HD disposal. Decontamination with any of the various chemical solutions currently in use by the army may result in the production of intermediates of varying toxicities. Experimental or proposed novel decontamination methods are not considered here.

We identified products associated with each of the degradation processes from field and laboratory studies as well as from analyses of stored containers. We then assessed the persistence and toxicities, both mammalian and environmental, of the degradation products.

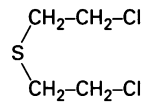
We obtained the information in this review through an extensive literature search. Searches of the following computerized databases were updated as of July/August 1997: Medline [National Library of Medicine (NLM), National Institutes of Health, Bethesda, MD], Toxline (NLM), Defense Technical Information Center (DTIC; Washington, DC), and Registry of Toxic Effects of Chemical Substances (RTECS; National Institute of Occupational Safety and Health/NLM). Searches of Current Contents (Institute for Scientific Information, Philadelphia, PA) continued through May 1999. Although we sought information on all identified degradation products, we placed emphasis on those products or contaminants identified as present in storage containers at concentrations of > 0.1%. The chemical nomenclature in this paper is based on nomenclature in ChemID (NLM). We do not present toxicity data for inorganic degradation products or for well-characterized organic entities such as ethanol or isopropyl alcohol.

Data on environmental fate, mammalian toxicity, and ecotoxicity are often lacking or minimal for many of the minor degradation products and contaminants identified in this paper. In addition, much of the data are historic or incompletely reported by contemporary standards. Evaluation of those degradation products and contaminants for which both environmental fate and toxicity information are available indicates that relatively few degradation products are persistent over long periods in the environment, and most of those that are persistent exhibit moderate-to-low levels of mammalian toxicity.

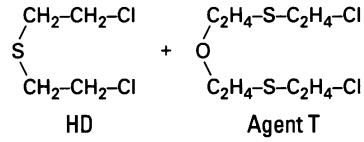
Vesicant Agents

Sulfur Mustard

Most of the following discussion of sulfur mustard refers to the chemical agent HD (shown below), which is a distilled or purified form of sulfur mustard.



HT (shown below) was made by an older manufacturing process and contains about 60% HD, < 40% agent T {bis[2-(2-chloroethylthio)ethyl] ether}, and a variety of sulfur contaminants and impurities.



HT may have many of the same toxic effects as HD. However, very few studies specific for agents HT or T were found in the available literature. Most laboratory studies of sulfur mustard are based on relatively pure mustard (HD) and not on undistilled sulfur mustard (H), which contains additional impurities. Sulfur mustard manufactured by older processes, such as the Levinstein process, contains 62–64% HD, whereas a 1-ton container of HD manufactured after World War II contains 89% HD (*13*). (Table 1 shows the chemical and physical properties of HD and HT.)

The U.S. unitary chemical weapons stockpile includes sulfur mustard stored in ton containers at Anniston Army Depot in Alabama, Umatilla Depot Activity in Oregon, Pine Bluff Arsenal in Arkansas, Tooele Army Depot in Utah, and Aberdeen Proving Ground in Maryland (*25*). HD, H, and HT are stored as nonstockpile chemical materials in various containers and munitions at these and several other sites.

Formation of degradation products. The fate of HD in the environment is based on its chemical and physical properties as well as on observations of persistence and degradation products from both field and laboratory studies. Information on degradation products, impurities, and stabilizers was also gleaned from analysis of the composition of the contents of ton containers that have been used to store HD. Weapons-grade agents can contain stabilizers, starting materials, or by-products formed during manufacturing, and products formed from slow reactions during storage. The degradation products, impurities, and stabilizers of HD are listed in Table 2 with synonyms and Chemical Abstract Service (CAS) numbers (*13,21,23, 26–29*). As previously noted, inorganic degradation products and well-characterized organic entities such as ethanol and isopropyl alcohol are not listed. Although listed, no effort was made to characterize toxicity for products present at < 0.1% in ton containers.

We were able to locate few data on the fate of HD in air in our literature search. The vapor pressure of HD is low [0.11 mmHg at 25°C (*30*)], but is sufficient for mustard to be in the air immediately surrounding droplets of the liquid. At moderate temperatures (25°C), HD deposited on the surface of soil will evaporate within 30–50 hr, depending on weather conditions (*8,31*). Because HD does not absorb ultraviolet (UV) radiation above 290 nm (*32*), photodegradation does not appear to be a significant degradative process (*16*). Atkinson (*33*) reported on the estimated rate constants of reactions of OH radicals with organic compounds. Using Atkinson's data (*33*), the Syracuse Research Corporation calculated that in the presence of $5 \times 10^5/cm^3$ photochemically produced hydroxyl radicals in the atmosphere (assumed average concentration in nonsmog conditions), HD will react with an estimated rate constant of 11.4×10^{-12} $cm^3/mol/sec$ at 25°C or a half-life of 1.4 days (*16*). No data on actual photodegradation or reaction rates in the atmosphere were located.

A Henry's Law constant of 2.4×10^{-5} $atm \times m^3/mol$ (*8*) indicates that volatilization from water could be significant. However, in the absence of turbulence and at low temperatures, large quantities of HD would persist under water for considerable periods and retain blister-forming properties (*34*).

Epstein et al. (*35*) reported that HD spilled into seawater would probably sink (specific gravity, 1.27 at 20°C) and remain on the bottom, where it would slowly dissolve, resulting in no more than a few parts per million of unhydrolyzed mustard in the supernatant water. Some of the agent might form a surface film on the water, where it would be removed within a few days by hydrolysis and volatilization (*35,36*). High levels of chlorine in the water inhibit hydrolysis; therefore, hydrolysis in seawater is slower than in freshwater (*35*).

The primary environmental fate mechanism of stored or buried HD is hydrolysis. Although HD is rapidly hydrolyzed [half-life of 4–8 min at 25°C in distilled water has been reported (*37*)], its rate is limited by the slow rate of solution. In addition, intermediate hydrolysis products that coat droplets of mustard may retard hydrolysis. Because of the low water solubility of HD and formation of intermediate products, bulk amounts of HD may persist undispersed under water for some time. For these reasons, sulfur mustard is considered fairly persistent in the environment.

Hydrolysis is surface controlled, with products formed at the HD–water interface and then diffused into the bulk water phase (*5,8,13,27,29*). The hydrolysis mechanism is

Table 2. Degradation products and impurities of sulfur mustard agent.

Names/synonyms	Formula	CAS no.	Source
Hemisulfur mustard (CH) Mustard chlorohydrin 2-Hydroxyethyl 2-chloroethyl sulfide 2-[(2-Chloroethyl)thio]ethanol	C_4H_9ClOS	693-30-1	Hydrolysis of sulfur mustard
Thiodiglycol (TDG) 2,2′-Thiobisethanol 2,2′Thiodiethanol Thiodiethylene glycol	$C_4H_{10}O_2S$	111-48-8	Hydrolysis of sulfur mustard
Bis(2-hydroxyethyl)-2-(2-chloroethylthio) ethyl sulfonium chloride Sulfur mustard–thiodiglycol aggregate HD-TDG or H1TG	$C_8H_{18}ClO_2S_2$•Cl	64036-91-5	Hydrolysis of sulfur mustard
Bis(2-hydroxyethyl)-2-(2-hydroxyethylthio) ethyl sulfide Hemimustard–thiodiglycol aggregate CH-TDG	$C_8H_{19}S_2O_3$	64036-92-6	Hydrolysis of sulfur mustard
Bis-2[bis(2-hydroxyethyl)-sulfonium ethyl] sulfide dichloride Sulfur mustard–thiodiglycol –thiodiglycol aggregate HD-TDG-TDG or H2TG	$C_{12}H_{28}O_4S_3$•2Cl	64036-79-9	Hydrolysis of sulfur mustard
Mustard sulfoxide 1,1′-Sulfinylbis(2-chloroethane) Bis(2-chloroethyl) sulfoxide	$C_4H_8Cl_2OS$	5819-08-9	Oxidation of sulfur mustard
Mustard sulfone 1,1′-Sulfonylbis(2-chloroethane) Bis(2-chloroethyl) sulfone	$C_4H_8Cl_2O_2S$	471-03-4	oxidation of mustard sulfoxide
2-Chloroethyl vinyl sulfide 2-Chloroethylthio ethene	C_4H_7ClS	81142-02-1	Dechlorination of sulfur mustard, decontamination with DS-2
Divinyl sulfide Ethylthioethene	C_4H_6S	627-51-0	Dechlorination of sulfur mustard, decontamination with DS-2
2-Chloroethyl vinyl sulfoxide	C_4H_7ClOS	40709-82-8	Dechlorination of sulfur mustard
Vinyl sulfoxide Divinyl sulfoxide 1,1-Sulfinylbis ethene	C_4H_6OS	1115-15-7	Dehydrochlorination of mustard sulfone
2-Hydroxyethyl vinyl sulfide 2-Vinylthioethanol 2-(Ethenylthio)ethanol	C_4H_8OS	3090-56-0	Dechlorination of hemimustard by DS-2, present in CaOH hydrolysate of H
2-Chloroethyl vinyl sulfone	$C_4H_7ClO_2S$	7327-58-4	Dechlorination of mustard sulfone
Divinyl sulfone	$C_4H_6O_2S$	77-77-0	Dechlorination of mustard sulfone
1,4-Dithiane Diethylene disulfide	$C_4H_8S_2$	505-29-3	Impurity, thermal decomposition, dechlorination of sulfur mustard, present in ton containers
1,4-Oxathiane 1,4-Thioxane	C_4H_8OS	15980-15-1	Dechlorination of hemimustard, present in ton containers
Bis[2-(2-chloroethylthio)ethyl] ether Agent T	$C_8H_{16}Cl_2OS_2$	63918-89-8	Impurity of sulfur mustard
1,2-Bis(2-chloroethylthio) ethane Compound Q Sesquimustard	$C_6H_{12}Cl_2S_2$	3563-36-8	Impurity, present in ton containers
1,2-Bis(2-hydroxyethylthio) ethane Q-diol	$C_6H_{14}O_2S_2$	NA	Hot water hydrolysis of sulfur mustard
Chloroform	$CHCl_3$	67-66-3	Incomplete reaction with STB
1,8-Dichloro-3-oxa-6-thiaoctane	$C_6H_{12}Cl_2OS$	NA	Impurity
Tetrachloroethylene	C_2Cl_4	127-18-4	Present in ton containers
Hexachloroethane	C_2Cl_6	67-72-1	Present in ton containers
2-Chloroethyl 3-chloropropyl sulfide	$C_5H_{10}Cl_2S$	71784-01-5	Present in ton containers
2-Chloroethyl 4-chlorobutyl sulfide	$C_6H_{12}Cl_2S$	114811-35-7	Present in ton containers
2-Chloroethyl (2-chloroethoxy)ethyl sulfide	$C_6H_{12}Cl_2OS$	114811-38-0	Present in ton containers
Bis(2-chloroethyl) disulfide Sulfur mustard disulfide	$C_4H_8Cl_2S_2$	1002-41-1	Impurity, present in ton containers
Bis(2-chloropropyl) sulfide	$C_6H_{12}Cl_2S$	22535-54-2	Impurity, present in ton containers
1,2-Dichloroethane	$C_2H_4Cl_2$	107-06-2	Impurity, present in ton containers
1,2,5-Trithiepane	$C_4H_8S_3$	6576-93-8	Present in ton containers
1,2,3,4-Tetrathiane	$C_2H_4S_4$	NA	Present in H
1,1,2,2-Tetrachloroethane	$C_2H_2Cl_4$	79-34-5	Present in ton containers
Bis(2-chloroethyl) trisulfide Sulfur mustard trisulfide	$C_4H_8Cl_2S_3$	19149-77-0	Impurity, present in ton containers
1,2,3-Trithiolane	$C_2H_4S_3$	NA	Impurity, present in ton containers
Sulfur mustard tetrasulfide	$C_4H_8Cl_2S_4$	NA	Present in ton containers
2-Methyl-1,3-oxathiolane	C_4H_8OS	NA	Present in CaOH hydrolysate of H
1-Oxa-4,5-dithiacycloheptane	$C_4H_8OS_2$	NA	Present in CaOH hydrolysate of H
2-Methyl 1-propene Methylpropene Isobutylene	C_4H_8	115-11-7	Present in ton containers
Thiirane Ethylene sulfide	C_2H_4S	420-12-2	Present in ton containers
2-Chlorobutane sec-Butyl chloride	C_4H_9Cl	78-86-4	Present in ton containers
Trichloroethylene	C_2HCl_3	79-01-6	Present in ton containers
Q sulfonium 1-(2-Chloroethyl) 1,4-dithanium chloride 1-(2-Chloroethyl)-1-thiona-4-thiane chloride	$C_6H_{12}ClS_2$•Cl	30843-67-5	Residue in ton containers

Abbreviations: CaOH, calcium hydroxide; DS-2, decontamination solution 2 (diethylenetriamine, 2-methoxyethanol, and sodium hydroxide); NA, not available; STB, supertropical bleach (a calcium hypochlorite-containing solution). Data from Rosenblatt et al. (*13*), NRC (*21*), Amr et al. (*23*), D'Agostino and Provost (*26*), MacNaughton and Brewer (*27*), Kingery and Allen (*28*), and Yang et al. (*29*).

complex and, depending on the availability of water, occurs by two routes, both of which lead to formation of thiodiglycol (TDG) and hydrochloric acid (Figure 1). In a dilute aqueous solution, dissolved HD is rapidly converted first to a sulfonium ion and then to the hemimustard and TDG. In the presence of insufficient water to initially dissolve all available HD, several sulfonium ion aggregates (TDG–mustard aggregates) are formed at the water–HD interface. Although Small (*8*) predicted that the sulfonium ion aggregates are too chemically unstable to be of environmental concern, Yang et al. (*29*) noted that they are stable products in water at ambient temperatures and would shield the bulk of the material from further dissolution. Thus, the formation of aggregates probably contributes to the environmental persistence of HD. As shown in Figure 1, hydrolysis of the hemimustard–TDG aggregate releases TDG. Although the reactions shown are reversible, Small (*8*) stated that the conditions required to produce reversible hydrolysis would not normally be encountered in the environment. In several studies compiled by Small (*8*), the hydrolysis half-life of dissolved HD ranged from 158 min at 0.6°C to ~ 1.5 min at 40°C and did not vary appreciably in the typical environmental pH range.

The U.S. Army has conducted a sampling and analysis (by gas chromatography) of ton containers of HD stored at Aberdeen Proving Ground (APG), Maryland (*38*) [reviewed by the National Research Council (NRC) (*21*) and Amr et al. (*23*)]. The HD stored at APG contains approximately 8.5% impurities formed either during manufacture or from decomposition of the HD during storage. In addition to HD, compounds present in the greatest amounts were 1,2-bis(2-chloroethylthio)ethane, hexachloroethane, 1,4-dithiane (estimated at 40 lb/container), 2-chloroethyl 3-chloropropyl sulfide, and 2-chloroethyl 4-chlorobutyl sulfide (Table 2). A residue in the bottom of the containers was composed primarily of 1-(2-chloroethyl)-1-thiona-4-thiane chloride (Q-sulfonium) formed by a reaction of HD with the metal on the inside of the ton containers or from a reaction with metal impurities during the manufacturing process of the agent (*23*). HD may form metal complexes with storage containers (HD-$FeCl_2$) or with the metal sulfides present in soil (*8*). Additional compounds identified in the containers are listed in Table 2. Trace metals were also present in the APG ton containers. The impurities 1,2-dichloroethane, trichloroethylene, tetrachloroethylene, 1,1,2,2-tetrachloroethane, and hexachloroethane may be subject to state and federal hazardous waste regulations.

D'Agostino and colleagues (*26,39–41*) used several methods to detect and identify mustard-related hydrolysis compounds. D'Agostino and Provost (*26*) used capillary column isobutane chemical ionization mass spectrometry to identify the compounds and impurities in munitions-grade HT, crude mustard containing ~ 15% carbon tetrachloride, and HQ (75% distilled mustard and 25% sesquimustard). In addition to sulfur mustard, which comprised 54, 74, and 82% of the three samples, respectively, sesquimustard, agent T, 1,4-oxathiane, 1,4-dithiane, and 2-chloroethyl (2-chloroethoxyl)ethyl sulfide ($C_6H_{12}OCl_2S$) were major components of the HT sample. The interpretation of chromatographic, mass spectral, trimethylsilyl derivatization, and gas chromatography-Fourier transform infrared spectroscopy data led to the characterization of a number of additional compounds including ether/thioether macrocycles and vinyl alcohols (not listed in Table 2) (*40*).

D'Agostino and Provost (*39*) identified the hydrolysis products of munitions-grade T, HT, HQ, and the longer-chain sulfur vesicants 2-chloroethyl (2-chloroethoxy)ethyl sulfide (CAS No. 114811-38-0; Table 2) and sesquimustard, after overnight hydrolysis at 50°C. Under these conditions, the primary products of HT and HQ were TDG, hemisulfur mustard, bis[(2-hydroxyethylthio)ethyl] ether, 2-chloroethyl (2-hydroxyethylthio)-ethyl ether, bis(2-hydroxyethylthio)ethane, mustard agent, and 1,4-dithiane. These authors had previously identified many of the same components of mustard samples (*26*) as those listed by Amr et al. (*23*) and the NRC (*21*).

D'Agostino and Provost (*39*) further characterized the hydrolysis pathways of chemicals other than HD that might be present in storage containers or in the environment. As noted, mustard hydrolysis resulted in production of the hemisulfur mustard and TDG. After hydrolysis of the impurity [2-chloroethyl (2-chloroethoxy)ethyl sulfide], the partial hydrolysis product [2-chloroethyl (2-hydroxyethylthio)ethyl ether] was tentatively identified. For sesquimustard, the partial and full hydrolysis products, 2-chloroethyl (2-hydroxyethylthio)ethyl sulfide and

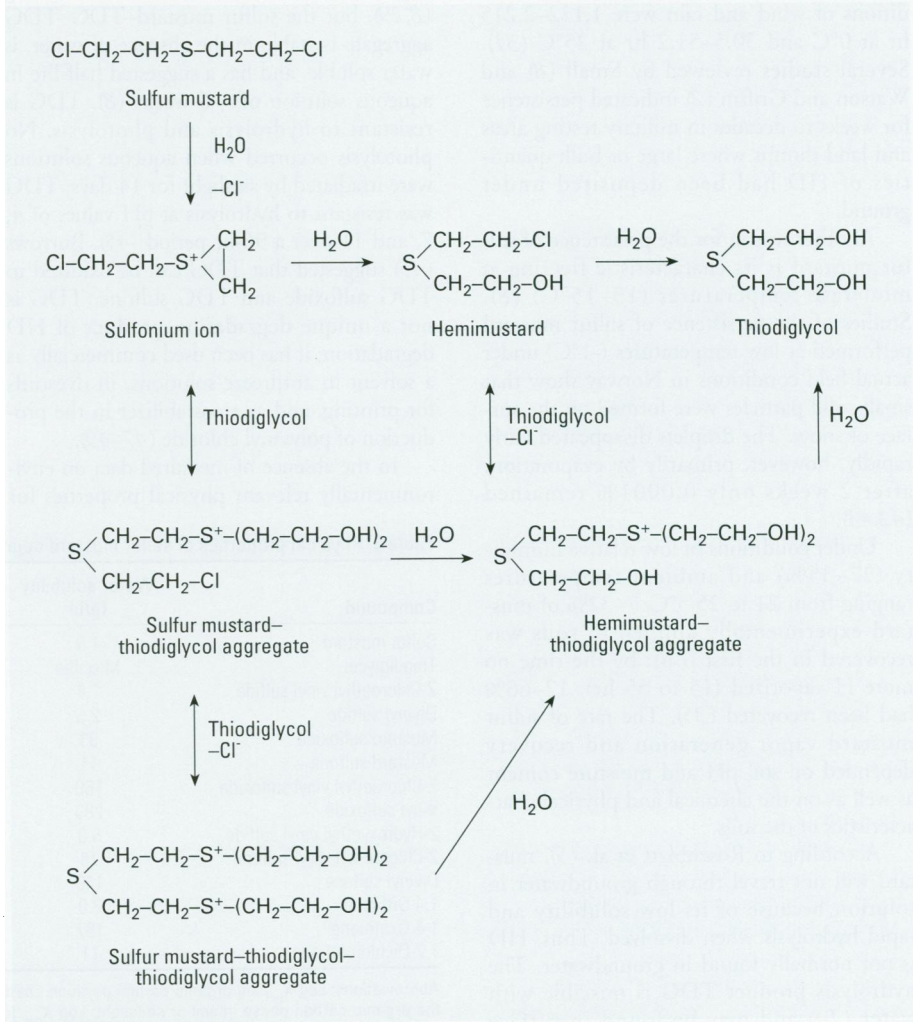


Figure 1. Primary hydrolysis pathways of sulfur mustard in the environment.

bis(2-hydroxyethylthio)ethane, respectively, were detected. For agent T, the partial and full hydrolysis products, 2-chloroethylthio)ethyl (2-hydroxyethylthio)ethyl ether and bis[(2-hydroxyethylthio)ethyl] ether, respectively, were detected. More recently, D'Agostino et al. (*41*) used packed capillary liquid chromatography-electrospray mass spectrometry to identify five longer-chain diols, two partial hydrolysis products, and three ether/thioether macrocycles as degradation products of sulfur mustard, sesquimustard, and agent T.

Sulfur mustard is lost from the soil surface primarily by evaporation, whereas mustard buried deep in the soil, where it cannot vaporize or undergo weathering, can remain undecomposed for years (*8*). Volatilization from soil was related to temperature, wind speed, and soil type. Droplets deposited on surfaces evaporate slowly, whereas bulk quantities remain where they were initially deposited during cool weather or under winter/arctic conditions. Predicted persistence times for drops applied to soil (nominal surface density of 50 g/m^2) under various conditions of wind and rain were 1,122–2,215 hr at 0°C and 30.5–51.2 hr at 25°C (*31*). Several studies reviewed by Small (*8*) and Watson and Griffin (*2*) indicated persistence for weeks to decades in military testing areas and land dumps where large or bulk quantities of HD had been deposited under ground.

Another reason for the persistence of sulfur mustard is its characteristic freezing at moderate temperatures (13–15°C) (*8*). Studies of the persistence of sulfur mustard performed at low temperatures (-1°C) under actual field conditions in Norway show that small solid particles were formed on the surface of snow. The droplets disappeared fairly rapidly, however, primarily by evaporation; after 2 weeks only 0.0001% remained (*42,43*).

Under conditions of low relative humidity (27–35%) and ambient temperatures ranging from 21 to 25.5°C, 7–32% of mustard experimentally applied to soils was recovered in the first 6 hr; by the time no more H vaporized (15 to 55 hr), 12–66% had been recovered (*35*). The rate of sulfur mustard vapor generation and recovery depended on soil pH and moisture content as well as on the chemical and physical characteristics of the soils.

According to Rosenblatt et al. (*5*), mustard will not travel through groundwater in solution because of its low solubility and rapid hydrolysis when dissolved. Thus, HD is not normally found in groundwater. The hydrolysis product TDG is miscible with water (*14*) and may be found in surface water or may leach into groundwater.

Theoretically, HD can be biodegraded in soil via the thioether oxidation pathway to form bis(2-chloroethyl) sulfoxide and the corresponding sulfone, which are both water insoluble (*44*). Morrill et al. (*44*) noted that mustard can also be biodegraded by reductive dehalogenation and dehydrohalogenation, although these pathways are predicted to be very slow. Although the above biodegradation pathways have been suggested, biodegradation of mustard has not been achieved under laboratory conditions, probably because of its toxicity to microorganisms. Thus, the major disappearance pathways would be hydrolysis in soil, due to soil moisture, and evaporation at the soil surface.

We located few data on the chemical and physical properties of the degradation products of sulfur mustard. Dissolved sulfur mustard would be rapidly hydrolyzed to HCl and TDG. However, the presence of degradation products in stored ton containers and in soil and/or groundwater indicates the persistence of some of the intermediates. Information on the stability of several of the sulfonium ion aggregates in the environment is conflicting (*8,29*), but the sulfur mustard–TDG–TDG aggregate is stable in the absence of water, is water soluble, and has a suggested half-life in aqueous solution of ~ 6 weeks (*8*). TDG is resistant to hydrolysis and photolysis. No photolysis occurred when aqueous solutions were irradiated by sunlight for 14 days; TDG was resistant to hydrolysis at pH values of 4, 7, and 11 over a 96-hr period (*45*). Burrows (*46*) suggested that TDG can be oxidized to TDG sulfoxide and TDG sulfone. TDG is not a unique degradation product of HD degradation; it has been used commercially as a solvent in antifreeze solutions, in dyestuffs for printing, and as a costabilizer in the production of polyvinyl chloride (*47–49*).

In the absence of measured data on environmentally relevant physical properties for many of the degradation products, Small (*8*) calculated physical properties for degradation products of sulfur mustard predicted to be stable in the environment. These properties are the octanol/water partition coefficient (K_{ow}), the affinity of a compound for the organic phase of the environment and thus the affinity to bioaccumulate; the soil absorption coefficient (K_{oc}), which is a measure of adsorption to the organic fraction of soil or sediment; water solubility; and vapor pressure (Table 3). Small (*8*) cautioned that predictive equations for several of these parameters are empirical and deviations of an order of magnitude from measured values may occur. The physical properties for the parent sulfur mustard compound are included for comparison purposes. In addition, Berkowitz et al. (*50*) compiled data on 1,4-oxathiane. Because of its similar chemical structure, the behavior of 1,4-oxathiane in the environment should be similar to that of 1,4-dithiane, with 1,4-oxathiane being more volatile and more water soluble. No dissociation constants (pK_a), an indicator of adsorption by sediments, were located for the chemicals in Table 3.

Several of the compounds are moderately-to-highly soluble in water (> 1 g/L), as shown in Table 3. Vapor pressures are generally low and indicate little volatility, with the possible exception of the vinyl sulfides and 1,2-dichloroethane. Log K_{oc} values of approximately ≤ 2 indicate that little soil adsorption will occur. Small (*8*) used the calculated physical properties to derive physical indices including persistence or removal by several processes. The derivations were based on water solubility and, for illustrative purposes, assumed a fractional soil organic carbon content of 0.02. According to Small (*8*), the leaching index, which he defines as the number of leachings required to reduce a compound to one-tenth of its initial concentration, was high for sulfur mustard and

Table 3. Physical properties of sulfur mustard degradation products.[a]

Compound	Water solubility (g/L)	Log K_{ow}	Log K_{oc}	Vapor pressure (mmHg)
Sulfur mustard	1.0	1.37	2.12	0.1
Thiodiglycol	Miscible	-0.77	0.96	0.00002
2-Chloroethyl vinyl sulfide	1.4	1.11	1.98	5.8
Divinyl sulfide	2.5	0.85	1.84	6.0
Mustard sulfoxide	93	-0.85	0.91	0.65
Mustard sulfone	11	-0.51	1.11	0.96
2-Chloroethyl vinyl sulfoxide	160	-1.11	0.77	0.064
Vinyl sulfoxide	280	-1.37	0.63	0.92
2-Hydroxyethyl vinyl sulfide	5.0	0.53	1.66	3.8
2-Chloroethyl vinyl sulfone	78	-0.77	0.96	0.023
Divinyl sulfone	140	-1.03	0.82	0.09
1,4-Dithiane	3.0	0.77	1.80	0.80
1,4-Oxathiane[b]	167	0.60	ND	3.9
1,2-Dichloroethane	11	1.48	2.18	8.5

Abbreviations: Log K_{oc}, log organic carbon partition coefficient, an estimate of the tendency of a chemical to adsorb to the organic carbon phase in soil or sediment; Log K_{ow}, log octanol/water partition coefficient, an estimate of a chemical's tendency to bioaccumulate in organisms; ND, not determined.
[a]Modified from Small (*8*), except for data on 1,4-oxathiane. [b]Data from Berkowitz et al. (*50*).

1,2-dichloroethane, indicating little leaching, whereas values for 2-chloroethyl vinyl sulfide, divinyl sulfide, 2-hydroxyethyl vinyl sulfide, and 1,4-dithiane were intermediate, indicating a moderate amount of leaching. The volatility potential estimates (the loss of a compound from soil) ranged from practically none for TDG to 2.3 days for divinyl sulfide and 1.8 years for HD. Calculated Henry's Law constants, a measure of volatilization from surface water, indicate that TDG, 2-chloroethyl vinyl sulfoxide, vinyl sulfoxide, 2-chloroethyl vinyl sulfone, and divinyl sulfone are essentially nonvolatile, whereas divinyl sulfide and 1,2-dichloroethane rapidly volatilize. The other compounds were calculated to be of intermediate volatility.

Two common degradation products of HD that persist in the environment are 1,4-oxathiane and 1,4-dithiane. 1,4-Oxathiane is formed by dehydrohalogenation of partially hydrolyzed mustard, whereas 1,4-dithiane is a thermal degradation product of mustard formed by dechlorination. Formation of dithiane occurs very slowly at ambient temperatures. 1,4-Oxathiane in soil may also be formed by rearrangement of 2-hydroxyethyl vinyl sulfide (*8*). Both products are groundwater contaminants in the Rocky Mountain Arsenal area near Denver, Colorado (*34*).

Pure 1,4-dithiane is a volatile crystalline organosulfur compound. Because of its moderate water solubility (3–12 g/L) and low K_{oc} (*8,50,51*), 1,4-dithiane leaches through soil to groundwater. Concentrations as high as 9 mg/L have been found at the Rocky Mountain Arsenal. Preliminary sampling results identified it in groundwater at APG (*51*). The estimated vapor pressure (0.8 mmHg) and Henry's Law constant (4.2×10^{-5} atm × m^3/mol) of 1,4-dithiane are sufficiently high to allow some vapor transport from soil and water to air. It readily photooxidizes to sulfoxides and sulfones (*51*).

In light of the selection of chemical neutralization followed by biodegradation of the hydrolysis products, the biodegradation of hydrolysis products is relevant. Two strains of the bacterial species *Pseudomonas pickettii* (SH18) and *Alcaligenes xylosoxidans* (ssp. *xylosoxidans* strain SH42) were isolated from areas purported to have been previously contaminated with HD. Both strains were killed by HD in culture. However, these strains were capable of using TDG as their sole source of carbon for growth (*29,52,53*). When mustard was hydrolyzed before inoculation with the bacteria, up to 97% of the carbon-containing hydrolysis products were degraded. Lee et al. (*54*) reported that TDG was completely degraded by *A. xylosoxidans* strain SH91 in laboratory-scale stirred-tank reactors. TGD added to various soils was oxidized to (2-hydroxyethyl)thio acetic acid and then to thiodiglycolic acid; biotransformation kinetics depended on soil type (zero-order rate coefficients ranged from 0 to 6.26 $\times 10^{-6}$ mol/L/hr for six soil types) (*45*).

The environmental stability of several of the degradation products allows monitoring of the use or presence of CW agents. For example, TDG, 2-hydroxyethyl vinyl sulfide, 1,4-dithiane, 1,4-oxathiane, and divinyl sulfide were among compounds identified in soil, munition fragments, and wool samples associated with a CW incident in Iraq. Twenty-three mustard-related compounds were tentatively identified along with the explosives 2,4,6-trinitrotoluene and tetryl (*55,56*). In addition to sulfur mustard (the primary component), sesquimustard, and agent T, 15 additional components including dehydrochlorination products were identified in an Iran–Iraq soil sample suspected to have been contaminated with mustard (*26*).

Decontamination. Decontamination solution 2 (DS-2; composed of diethylenetriamine, ethylene glycol monomethyl ether, and sodium hydroxide), and supertropical bleach (STB; a hypochlorite-containing solution) are the most commonly used decontaminant solutions for CW agents (*8*). For HD, decontamination procedures produce many of the same products observed during hydrolysis. Reaction of HD with DS-2, which acts as a "superbase," is rapid at 25°C. If the reaction is complete, only divinyl sulfide, formed through two elimination reactions, will be produced. If the reaction is incomplete, divinyl sulfide, 2-chloroethyl vinyl sulfide, TDG, and possibly 2-hydroxyethyl vinyl sulfide are formed (*8,29*).

Decontamination of HD with hypochlorite-containing materials such as calcium hypochlorite or STB results in essentially complete mineralization to carbon dioxide, water, and inorganic substances if the reaction is complete (*8,13,57*). Incomplete reaction may result in the formation of the intermediates mustard sulfoxide, mustard sulfone, and chloroform. The reaction pathway with hypochlorite was outlined by Yang et al. (*29*) and Small (*8*). Mustard sulfoxide is formed first, followed by mustard sulfone; these oxidation products undergo elimination reactions to produce the corresponding monovinyl and divinyl sulfoxides and sulfones. Small amounts of other unidentified oxidation products are also present in the final solution. The pathway is similar in the presence of other oxidants such as hydrogen peroxide (*5*). Likewise, in the presence of the commercial mixture Oxone (DuPont, Newark, DE; potassium peroxysulfate), HD is oxidized immediately to the sulfoxide, which converts more slowly to the sulfone (*29*). 1,4-Dithiane is readily photooxidized in water and will probably be oxidized by various oxidants in water (*50*). Addition of organic solvents such as acetone to solubilize HD appears to decrease the rate of formation of the sulfonium ion intermediates and accelerate hydrolysis (*13,37*).

The Army Chemical Stockpile Disposal Program (APG, MD) has chosen chemical neutralization [hot water hydrolysis followed by photochemical oxidation of hydrolysate to remove volatile organic compounds (VOCs) and subsequent biodegradation] as an alternative technology to incineration for chemical demilitarization of HD stored in ton containers at APG (*21,23,24,58*). The hydrolysis process destroys the HD and forms primarily TDG and chlorinated VOCs. In laboratory studies that tested various conditions of temperature, HD concentration, and sodium hydroxide concentration, HD was completely hydrolyzed to TDG, ethers, and thioethers (*53*). According to Amr et al. (*23*), the hot water hydrolysate after 3.8% agent loading is typically composed of water (~ 90%), TDG (~ 5%), HCl (~ 3%), sulfonium ions (~ 1%), 1,2-bis(2 hydroxyethylthio) ethane (0.2%), and 1,4-dithiane (0.12%), with other constituents present at < 0.1%. The hydrolysate is then sent to a biodegradation reactor containing ordinary sewage sludge, where more than 99% of the TDG is mineralized to carbon dioxide, water, and sulfate (*24*).

Acute and chronic mammalian toxicity. Sulfur mustard is a vesicant or blister agent that possesses strong alkylating properties and consequently demonstrates systemic toxicity in addition to its effects on skin, eyes, and respiratory tract (*2*). It also is considered a known human carcinogen (*59–61*). Some HD degradation products retain considerable toxicity including, in some cases, vesicant action. Examples include mustard and hemimustard–TDG aggregates, mustard sulfone, and divinyl sulfone. In general, compounds that have a 2-chloroethylsulfide moiety are alkylating agents that have vesicant action. These compounds can form the cyclic sulfonium intermediate that will yield alkylated products in a manner consistent with the toxic action of HD (*62*). Other compounds such as TDG exhibit low to very slight toxicity and do not retain the vesicant property.

Hydrolysis of HD results in a host of degradation products, but primarily TDG. Acute and chronic mammalian toxicity data are available only for a small number of these breakdown products. The acute mammalian toxicity data that we located for HD degradation products (*63–129*) are presented in Table 4; the chronic toxicity data are shown in Table 5. The emphasis is placed on relevant exposure routes (oral, dermal, and inhalation), but where no such data were available, we presented data for other routes.

TDG is relatively nontoxic upon acute exposure, requiring oral doses in the range of 4–6 g/kg to produce 50% lethality in rodents (Table 4). Thus, its oral acute lethality potency is approximately 0.0025 times that of HD in rats (*2*). TDG is a moderate eye irritant and mild skin irritant in rabbits (Table 4). It is an occupational eye, skin, and mucous membrane irritant, although no established regulatory criteria exist for occupational inhalation or dermal exposures to TDG. A recent subchronic study of the pure compound at doses of 0, 50, 500, or 5,000 mg/kg/day, 5 days/week, for 90 days yielded a no-observed-adverse-effect level (NOAEL) of 500 mg/kg/day in male and female rats. No lethality was observed at the highest dose tested, nor were there any visible signs of

Table 4. Effects of acute exposure to sulfur mustard degradation products and impurities.

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
Sulfur mustard hydrolysis			
Thiodiglycol ($C_4H_{10}O_2S$; 111-48-8)	Rat: oral, 6,610 mg/kg (*63*) Guinea pig: oral, 3,960 mg/kg (*63*) Rabbit: skin, 20 mL/kg (*65*)		Rabbit: moderate eye irritant, 500 mg (*64*) Rabbit: mild skin irritant, 500 mg open (*65*)
Hemisulfur mustard (C_4H_9ClOS; 693-30-1)	Rat: im, 500 µg/kg (*66*) Mouse: skin, 600 mg/kg (*67*) Mouse: iv, 35 mg/kg (*67*)		
Bis-2[bis(2-hydroxyethyl)-sulfonium ethyl] sulfide dichloride ($C_{12}H_{28}O_4S_3$•2Cl; 64036-79-9)	Mouse: ip, 50 mg/kg (*68*)	Rat: oral, 250 mg/kg (*69*)	
Bis(2-hydroxyethyl)-2-(2-chloroethylthio)ethyl sulfonium chloride (sulfur mustard–thiodiglycol aggregate) ($C_8H_{18}ClO_2S_2$•Cl; 64036-91-5)	Rat: oral, 1,070 mg/kg (*70*) Rat: skin, 10–15 mg/kg (*67*) Mouse: skin, ~ 15 mg/kg (*67*) Dog, rabbit, skin, > 30 mg/kg (*67*) Rabbit: skin, 450 µL/kg (*70*)		Mouse, rabbit: skin, 0.5 and 1.0 × LD_{50} dose, moderate to severe enteritis, damage to lymphoid organs, especially spleen, mild to moderate adrenal congestion, mild liver necrosis (only at LD_{50} dose); negative for bone marrow damage. Species differences in adrenal and splenic effects (*67*)
Sulfur mustard decontamination			
Mustard sulfoxide ($C_4H_8Cl_2OS$; 5819-08-9)		Rat: 150 mg/kg, route unknown (*71*)	
Mustard sulfone ($C_4H_8SO_2Cl_2$; 471-03-4)	Rat: iv, > 72 mg/kg (*67*) Mouse: iv, 50 mg/kg (*67*) Rat: sc, 50 mg/kg (*67*) Mouse: sc, 35 mg/kg (*67*)	Cat: inhalation, 1,430 mg/m^3/10 min (*72*) Rabbit: inhalation, 1,430 mg/m^3/10 min (*72*)	
Divinyl sulfide (C_4H_6S; 627-51-0)	Rat: oral, 170 mg/kg (*73*) Mouse: oral, 112 mg/kg (*73*) Rat: inhalation, 660 mg/m^3 (*74*) Mouse: inhalation, 510 mg/m^3 (*74*)		
Thiodiglycol ($C_4H_{10}O_2S$; 111-48-8)	Rat: oral, 6,610 mg/kg (*63*) Guinea pig: oral, 3,960 mg/kg (*63*) Rabbit: skin, 20 mL/kg (*65*)		Rabbit: moderate eye irritant, 500 mg (*64*) Rabbit: mild skin irritant, 500 mg open (*65*)
2-Chloroethyl vinyl sulfoxide (C_4H_7ClOS; 40709-82-8)		Rat: oral, 100 mg/kg (*69*) Mouse: oral, 100 mg/kg (*75*)	
Divinyl sulfoxide (C_4H_6OS; 1115-15-7)		Rat: oral, 100 mg/kg (*69*) Mouse: oral, 50 mg/kg (*75*)	
Divinyl sulfone ($C_4H_6O_2S$; 77-77-0)	Rat: oral, 32 mg/kg (*76*) Rabbit: skin, 22 µL/kg (*76*)	Mouse: inhalation, 990 mg/m^3/10 min (*75*) Guinea pig: oral, 5 mg/kg (*78*)	Rabbit: moderate skin irritant, 50 mg open (*77*) Rabbit: severe skin irritant, 2 mg/24 hr (*79*) Rabbit: moderate eye irritant, 50 mg (*77*) Rabbit: severe eye irritant, 5 mg/24 hr (*79*)
1,4-Dithiane ($C_4H_8S_2$; 505-29-3)	Rat: oral, 3,473 mg/kg (*80*)	Rat: oral, 2,818 mg/kg (*80*)	Rat: ataxia, lacrimation, lethargy, crusty eyes and nose; gastrointestinal, lung, and liver (females only) (*80*)
1,4-Oxathiane (C_4H_8OS; 15980-15-1)	Rat: oral, 2,830 mg/kg (*81*) Rat: oral, 3,123 mg/kg (*80*) Rat: inhalation, 4,000 ppm/4 hr (*82*)		Rabbit: mild skin irritant, 10 mg/24 hr open (*81*) Rabbit: mild skin irritant, 500 mg/24 hr (*79*) Rabbit: eye irritant, 20 mg open (*81*) Rabbit: moderate eye irritant, 100 mg/24 hr (*79*)
Chloroform ($CHCl_3$; 67-66-3)	Rat: oral, 908 mg/kg (*83*) Mouse: oral, 36 mg/kg (*88*) Dog: oral, 1 g/kg (*90*) Guinea pig: oral, 830 mg/kg (*92*) Rat: inhalation, 47.7 mg/m^3/4 hr (*94*) Rabbit: dermal, > 20 g/kg (*96*)	Human: oral 2,514 mg/kg (*84*) Human: inhalation, 10 ppm/year (*89*) Human: inhalation, 1,000 mg/m^3/7 min (*76*) Human: inhalation, 5,000 mg/m^3/7 min (*93*) Dog: inhalation, 100 g/m^3 (*95*) Cat: inhalation, 35,000 mg/m^3/4 hr (*93*) Guinea pig: inhalation, 20,000 ppm/2 hr (*97*) Rabbit: inhalation, 59 g/m^3 (*95*) Rat: inhalation, 8,000 ppm/4 hr (*76*) Mouse: inhalation, 28 g/m^3 (*85*) Human: 546 mg/kg (*98*)	Human: eye, pain, irritation, and anesthesia, central nervous system depression, death from cardiac or respiratory arrest; liver and kidney damage (*85,86,87*) Rabbit: skin, irritant, 10 mg/24 hr (*76*) Rabbit: eye irritant, 148 mg (*91*)

continued, next page

toxicity. Measurable indicators of toxicity included decreased body weight, body weight gain, and kidney effects, but no histopathologic indicators of toxicity (*130*). Literature searches yielded no data pertaining to chronic or reproductive toxicity, genotoxicity, or carcinogenicity of TDG. The U.S. Army Center for Health Promotion and Preventive Medicine (APG, MD) has estimated reference dose (RfD) and reference concentration (RfC) values using the recent experimental subchronic rat NOAEL of 500 mg/kg/day and, for comparison, quantitative structure–activity relationships (QSARs), which are evaluated with TOPKAT software (Health Designs, Inc., Rochester, NY). Using this method, Bausum et al. (*190*) estimated a rat oral LD_{50} value of 2,700 mg/kg and a rat chronic oral lowest lethal dose (LD_{LO}) of 1,700 mg/kg for TDG. Use of the QSAR LD_{LO} resulted in an RfD estimate of 570 µg/kg/day, as compared to an RfD estimate of 500 µg/kg/day based on the NOAEL of 500 mg/kg/day from the subchronic oral toxicity study with rats (*190*). The recommended RfD value is 500 µg/kg/day.

Hemisulfur mustard is an intermediate formed in the course of HD hydrolysis to TDG; it retains some acute toxicity, being in the range of 0.1–0.25 times as toxic as HD in mice [comparing dermal as well as intravenous (iv) data (*67*)]. It exhibits some indications of genotoxicity (Table 5). This compound is not expected to persist in the environment but is further hydrolyzed very rapidly.

Acute toxicity data are available for only two other HD hydrolysis products. The oral toxicity of the sulfur mustard–TDG aggregate bis(2-hydroxyethyl)-2-(2-chloroethylthio)ethyl

Table 4. *Continued.*

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
Sulfur mustard contaminants in ton containers			
1,2-Bis(2-choroethylthio)ethane ($C_6H_{12}Cl_2S_2$; 3563-36-8)	Human: inhalation, 300 mg/min/m^3 (*99*) Dog: inhalation, 90 mg/m^3/2 min (*100*) Rat: inhalation, 66 mg/m^3/2 min; 11 mg/m^3/10 min (*100*) Mouse: inhalation, 36 mg/m^3/2 min; 6 mg/m^3/10 min (*100*) Guinea pig: inhalation, 110 mg/m^3/2 min; 8 mg/m^3/10 min (*100*) Hamster: inhalation, 137 mg/m^3/2 min; 22 mg/m^3/10 min (*100*) Pigeon: inhalation, 61 mg/m^3/10 min (*100*)		
O-sulfonium ($C_6H_{12}ClS_2$•Cl; 30843-67-5)	Mouse: ip, 75 mg/kg (*101*)		
Tetrachloroethylene (C_2Cl_4; 127-18-4)	Rat: oral, 2,629 mg/kg (*102*) Mouse: oral, 8,100 mg/kg (*104*) Rat: inhalation, 34,200 mg/m^3/8 hr (*102*) Mouse: inhalation, 5,200 ppm/4 hr (*107*)	Dog: oral, 4 g/kg (*103*) Cat: oral, 4 g/kg (*103*) Rabbit: oral, 5 g/kg (*103*)	Human: inhalation, 96 ppm/7 hr (local anesthetic) (*104*) Human: inhalation, 600 ppm/10 min, conjunctival irritation (*105*) Human: inhalation, 50 ppm/4 hr, visual system dysfunction (*106*) Human: child, oral, 545 mg/kg (coma) (*108*) Rabbit: severe skin irritant, 810 mg/24 hr (*109*) Rabbit: mild skin irritant, 500 mg/24 hr (*110*) Rabbit: mild eye irritant, 162 mg (*109*) Rabbit: mild eye irritant, 500 mg/24 hr (*110*)
Hexachloroethane (C_2Cl_6; 67-72-1)	Rat: oral, 4,460 mg/kg (*111*) Guinea pig: oral, 4,970 mg/kg (*111*) Rabbit: skin, 32 g/kg (*111*)	Rat: inhalation, 5,900 ppm/8 hr (*111*)	Rat: inhalation, 5,900 ppm/8 hr, muscle weakness (*111*)
Bis(2-chloropropyl sulfide) ($C_6H_{12}Cl_2S$; 22535-54-2)		Mouse: inhalation, 380 mg/m^3/10 min (*112*)	
1,2-Dichloroethane ($C_2H_4Cl_2$; 107-06-2)	Rat: oral, 670 mg/kg (*113*) Mouse: oral, 413 mg/kg (*115*) Dog: oral, 5,700 mg/kg (*118*) Rabbit: oral, 860 mg/kg (*121*) Monkey: inhalation, 3,000 ppm/7 hr (*110*) Rat: inhalation, 1,000 ppm/7 hr (*124*) Rabbit: skin, 2,800 mg/kg (*118*)	Human: oral, 286 mg/kg (*114*) Human: oral, 714 mg/kg (*116*) Pig: inhalation, 3,000 ppm/7 hr (*119*) Mouse: inhalation, 5 g/m^3/2 hr (*122*) Rabbit: inhalation, 3,000 ppm/7 hr (*119*) Guinea pig: inhalation, 1,500 ppm/7 hr (*119*)	Human: peripheral nervous system effects, coma, gastrointestinal tract effects, 4,000 ppm/1 hr (*95*) Human: eye, nose, throat irritation, high concentration (*117*) Cat, rat, monkey, rabbit: 1,000 ppm, ~ 7 hr/day, 5 days/week; fatty changes in liver (*120*) Rabbit: mild skin irritation, 625 mg open (*123*) Rabbit: mild skin irritation, 500 mg/24 hr (*110*) Rabbit: severe eye irritation, 63 mg (*123*)
1,1,2,2-Tetrachlorethane ($C_2H_2Cl_4$; 79-34-5)	Rat: oral, 250 mg/kg (*125*) Rat: oral, 400 mg/kg (*127*) Mouse: inhalation, 4,500 mg/m^3/2 hr (*129*)	Dog: oral, 300 mg/kg (*126*) Dog: oral, 700 mg/kg (*128*) Rabbit: 500 mg/kg (*128*) Rat: 1,000 ppm/4 hr (*82,129*) Mouse: 9 g/m^3/40 min (*93*) Cat, 19 g/m^3/45 min (*93*)	Human: behavioral symptoms, 1,000 g/m^3/30 min (*93*)

Abbreviations: im, intramuscular; ip, intraperitoneal; iv, intravenous; LC_{50}, median lethal concentration; LC_{LO}, lowest lethal concentration; LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose; sc, subcutaneous.

sulfonium chloride (HD-TDG) in rats is 0.017–0.02 times that of HD (Table 4). However, its dermal toxicity (lethality) is equivalent to that of HD in rats and higher than HD in mice and rabbits (*67*). Its iv lethality is also equivalent to that of HD in rabbits (*67*). We located only one data point for the sulfur mustard–TDG–TDG aggregate bis[bis(beta-hydroxyethyl)sulfonium ethyl] sulfide dichloride (HD–TDG–TDG) (*68*). An intraperitoneal (ip) LD_{50} value of 50 mg/kg in mice was reported in the literature (*68*) (Table 4); Anslow et al. (*67*) considered this compound to have relatively low toxicity but presented no supporting data. We found no chronic toxicity information for these or any HD hydrolysis products other than hemisulfur mustard.

We located toxicity data on several HD oxidation products that are formed by the incomplete reaction of HD with DS-2 (divinyl sulfide, 2-chloroethyl vinyl sulfide, TDG, and 2-hydroxyethyl vinyl sulfide) and with STB (mustard sulfoxide, mustard sulfone, and chloroform) (*8*). Divinyl sulfide is about 0.1 times as toxic to rats (oral exposure) as HD (Table 4) (*2*); in one test for embryotoxicity, it was reported to have no effect (*73*). We found no biologic data for 2-chloroethyl vinyl sulfide or for 2-hydroxyethyl vinyl sulfide. Ishidate et al. (*71*) reported an LD_{LO} value of 150 mg/kg in rats for mustard sulfoxide administered by an unspecified route. No chronic toxicity data were available for this compound. Acute inhalation exposure of cats and rabbits to mustard sulfone for 10 min resulted in an LC_{LO} value of 1,430 mg/m^3 for both species (*72*). Data were unavailable for other directly relevant routes of exposure, but Anslow et al. (*67*) reported subcutaneous (sc) LD_{50} values of 35 and 50 mg/kg for mice and rats, respectively, or approximately 0.1 times that of HD. The iv LD_{50} for the mouse is 50 mg/kg, whereas that for the rat is > 72 mg/kg, or approximately 0.17 and < 0.01 times that of HD, respectively (*67*). In our literature search we did not locate chronic toxicity data for mustard sulfone.

Table 4 contains limited acute toxicity data for three products of HD dechlorination: 2-chloroethyl vinyl sulfoxide, vinyl sulfoxide, and divinyl sulfone. The first two compounds appear to have similar oral lethality in mice and rats, although only LD_{LO} values are available. Historical values average 100 mg/kg except for the oral LD_{LO} of 50 mg/kg for vinyl sulfoxide in mice (*75*). Chronic toxicity data are unavailable for these substances. The oral LD_{50} value for divinyl sulfone in rats of 32 mg/kg (*76*) is just half the toxicity of HD (*2*). It is more toxic than mustard sulfone by factors of 2–5 in iv and sc tests in mice and rats [calculated from data presented by Anslow et al. (*67*)]. It is approximately equivalent to HD in mice by the iv and sc routes and only slightly less lethal than HD in rats by these routes (*67*). Genotoxicity tests with divinyl sulfone

Table 5. Carcinogenicity, genotoxicity, reproductive toxicity, and systemic effects of chronic exposure to sulfur mustard degradation products and impurities.

Degradation product (formula; CAS no.)	Carcinogenicity	Genotoxicity	Reproductive effects	Systemic effects
Sulfur mustard hydrolysis				
Thiodiglycol ($C_4H_{10}O_2S$; 111-48-8)				Rat: gavage, mildly decreased body weight and body weight gain, mild kidney effects, 5,000 mg/kg/day, 90 days (*130*)
Hemisulfur mustard (C_4H_9ClOS; 693-30-1)		DNA inhibition, other end points (*131*) DNA adduct formation: 100 µmol/L, rat liver; 4 mg/kg, mouse Ascites tumor (*132*)		
Sulfur mustard decontamination				
Divinyl sulfide (C_4H_6S; 627-51-0)			Embryotoxicity: negative (*73*)	
Divinyl sulfone ($C_4H_6SO_2$; 77-77-0)		Mutagenicity: negative, Ames test (*133*) Mutagenesis: positive, mouse lymphoma cells, 0.25 µg/mL (*134*) Dominant lethal: negative, male mouse (*135,136*) Micronucleus test: bone marrow, negative (*135*) Cytogenicity: positive (*137*)		
1,4-Dithiane ($C_4H_8S_2$; 505-29-3)		Mutagenesis: negative, Ames test with activation (*138*) Mutagenesis: low positive, Ames test without activation, negative with activation (*140*) SCE induction: CHO cells, negative with and without activation (*140*)		Rat: mild liver and kidney effects but no overt toxicity at doses up to 420 mg/kg/day, 90-day exposure (*139*)
1,4-Oxathiane (C_4H_8OS; 15980-15-1)		Mutagenesis: negative, Ames test with and without activation (*141*)		
Chloroform ($CHCl_3$; 67-66-3)	Probable human carcinogen (*142,143*) Rat: positive (*87*) Mouse: positive (*87*) Rat: positive, mouse: negative (*150*)	Mutagenicity: Ames, negative (*144*) Mutagenicity: yeast, positive (*146*) Mutagenicity: mouse, positive (*145*) Chromosome effects: human lymphocytes, negative (*151*) SCE: *in vitro*, low or negative (*152–154*) SCE: mouse, *in vivo*, positive (*154*) Micronucleus: negative (*155*) Delayed cell cycle: human lymphocytes, positive (*154*)	Rat: fetotoxic, retarded development, teratogenic (*145*) Mouse: sperm abnormalities (*147*) Mouse: negative in sperm morphology assay (*149*)	Human: hepatomegaly, fatty liver degeneration, toxic hepatitis (*87*) Human: central nervous system, psychiatric, neurologic effects (*148*)

continued, next page

in several systems yielded mostly negative results (Table 5). This compound was positive for mutagenesis in mouse lymphoma cells (*134*) but negative in the Ames test (*133*). It was also negative in a dominant lethal test in male mice (*135*) and in the bone marrow micronucleus test (*135*). It was positive for cytogenicity in a recent study by Choi et al. (*137*).

Two of the persistent thermal/hydrolysis degradation products of HD, 1,4-dithiane and 1,4-oxathiane, are present in groundwater at the Rocky Mountain Arsenal and have been identified in ton containers of HD. Acute toxicity data for 1,4-dithiane are very limited but suggest low acute lethality; the oral LD_{50} value for rats is about 3.5 g/kg (*80*) (Table 4). Mutagenicity tests in *Salmonella* gave negative or equivocal results (Table 5), and tests of sister chromatid exchange (SCE) in Chinese hamster ovary cells were negative both with and without metabolic activation (*140*). Subchronic exposure of rats to 1,4-dithiane resulted in anisotropic crystal induction (different properties along different axes) in the olfactory nasal mucosa and mild liver and kidney effects (*139*). The biologic significance of the anisotropic crystals is not understood.

The acute toxicity of 1,4-oxathiane also is relatively low, with oral LD_{50} values in rats of approximately 3 g/kg (*80,81*) (Table 4) and an inhalation LC_{LO} of 4,000 ppm/4 hr (*82*). This substance is a mild skin irritant and moderate eye irritant in rabbits (Table 4). 1,4-Oxathiane was negative for mutagenicity in the Ames test both with and without metabolic activation (*141*) (Table 5).

Two impurities of HD, one of which is present in the ton containers of HD, are warfare agents themselves: agent T and 1,2-bis(2-chloroethylthio)ethane (compound Q) (*99*). Robinson (*99*) estimated that the human LC_{50}–time relationship value for agent T (a vesicant) for inhalation exposure was 400 mg/min/m^3. This was probably based on animal data for HT; values for HT exposure ranged from 100–200 mg/min/m^3 for dogs to 3,000–6,000 mg/min/m^3 for guinea pigs and rabbits (*191*). Robinson (*99*) also estimated that the corresponding value for compound Q in humans was 300 mg/min/m^3; its action on the lungs resembled that of phosgene. The LC_{50} values for 2-min exposures to compound Q for several mammalian species range from 36 mg/m^3 in mice to 137 mg/m^3 in hamsters, with the value for dogs at 90 mg/m^3 (*100*). Another impurity, Q-sulfonium, which forms a residue on the bottom of ton containers, has an ip LD_{50} in mice of approximately 75 mg/kg and retains alkylating properties (*101*) (Table 4).

Chronic toxicity data were not available for compound Q or agent T. Chronic exposure to HT causes sensitization and chronic lung impairment (cough, shortness of breath, chest pain) (*191*), but sources provided no data specific for agent T. Again, chronic exposure to HT was said to be capable of causing birth defects (*191*), but we found no reproductive toxicity studies specific to agent T. Agent T was mutagenic in *Drosophila*, producing sex-linked lethal mutations with a potency equivalent to HD (*192*).

Bis(2-chloropropyl) sulfide is lethal in mice at 380 mg/m^3/10 min (*72*). We did not locate chronic toxicity data for bis(2-chloropropyl) sulfide, but it has been reported to cause DNA damage in chicken leukocytes *in vitro* (*189*).

Many other compounds, including solvents, are present at extremely low levels (< 1%) in ton containers of HD (*21*), but relevant toxicologic data have been identified for only a few of them. These chemicals are expected to be completely destroyed by

Table 5. *Continued.*

Degradation product (formula; CAS no.)	Carcinogenicity	Genotoxicity	Reproductive effects	Systemic effects
Sulfur mustard contaminants in ton containers				
Tetrachloroethylene (C_2Cl_4; 127-18-4)	Probable human carcinogen (*156*) Rat: positive, inhalation, leukemia, testicular tumors, kidney tumors (*160,161*) Mouse: positive, inhalation and oral, liver tumors (*160,161*)	Mutagenicity: generally negative (*157*) SCE: negative, chromosome aberration, negative, CHO cells (*162*) Human SCE: negative, nonsmokers; positive, smokers (*165*) Replicative DNA synthesis test (*166*)	Mouse: positive, several end points (*158*) Rat: positive, several end points (*158,163*)	Human: neurotoxicity (visuospatial function, memory, mood), < 50 ppm/ 3 years or more (*159*) Human: neurotoxicity (vigilance, reaction time, visual memory), 10.6 years (*164*)
Hexachloroethane (C_2Cl_6; 67-72-1)	Suspect human carcinogen (*167,168*) Rat: positive, oral (*171*) Mouse: positive, oral (*170*)	Mutagenicity: *Salmonella*, negative (*169*), SCE, CHO, positive (*162*) Chromosome aberrations: CHO, negative (*162*)	Rat: teratogenesis, negative (*111*)	Rat: oral, nephropathy (*170,171*) Mouse: oral, nephropathy (*170*)
1,2-Dichloroethane ($C_2H_4Cl_2$; 107-06-2)	Rat: positive, oral; mouse, positive, oral (*172*) Rat: negative, inhalation (*176*) B2, probable human carcinogen; induced several tumor types in rats and mice exposed by gavage, lung papillomas in mice formation after *in vivo* or when exposed by skin painting (*179*)	Mutagenicity: positive, Ames test (*173*) Mutagenicity: positive, human lymphoblastoid cells (*177*) Rat: DNA damage (*180*) Mutagenic in Ames test; induced somatic and germ cell mutations in *Drosophila*; metabolites caused DNA adduct *in vitro* exposure (*179,182*)	Rat, rabbits: negative, teratogenicity, embryotoxicity, reproduction performance (*174*) Rat: fertility effects (*178*) Rat: positive, embryonic growth retardation *in vivo* and *in vitro*; negative, teratogenicity (*181*)	Rat: negative, oral, 37.5–150 mg/kg/90 days (*175*)
1,1,2,2-Tetrachloroethane ($C_2H_2Cl_4$; 79-34-5)	Mouse: positive, oral Rat: negative, oral (*183*) Class C, possible human carcinogen (increased incidence of hepatocellular carcinomas in mice) (*184*)	Mutagenicity: negative in Ames test (*183*) Mutagenicity: positive, *Salmonella* (*185*) DNA repair: positive, *E. coli* (*187*) SCE: positive; chromosome aberrations, negative, CHO cells (*162*) Genotoxicity: positive, prophage lambda in *E. coli* (*188*) Mouse: positive, oral, 200 mg/kg replicative DNA synthesis test (*166*)		High concentrations induce narcosis, nephritis, toxic hepatitis, and liver atrophy (*98*) Rodents, fatty liver degeneration, changes in liver weight (*186*)
Bis(2-chloropropyl) sulfide ($C_6H_{12}Cl_2S$; 22535-54-2		Chicken: leukocyte, DNA damage (*189*)		

Abbreviations: SCE, sister chromatid exchange; CHO, Chinese hamster ovary.

the hot water neutralization/biodegradation disposal process for HD. The toxicity data for these chemicals are also presented in Tables 4 and 5.

Chloroform is a commonly used solvent with well-known toxicologic properties. It is a central nervous system (CNS) toxicant, which can cause lassitude and mental dullness in humans at 80–240 ppm and clinical anesthesia at 10,000 ppm (*167*). Death can result from respiratory depression, cardiac arrest, or liver toxicity associated with anesthetic use (*87,193*). Chloroform is a skin and eye irritant and causes corneal injury in humans (Table 4) (*76,194*). Liver and kidney damage can ensue after acute exposure (*87,195*). Chloroform is a suspected human carcinogen of moderate potency for lifetime oral exposure (*143,150,167*) (Table 5). Chloroform is metabolized via several pathways. The hepatotoxicity is due to oxidative dechlorination to phosgene, which binds to tissue proteins (*196*). Chloroform is fetotoxic and teratogenic in rats and produces sperm abnormalities in mice (*193*). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold-limit-value time-weighted average (TLV-TWA) for chloroform is 10 ppm (49 mg/m^3) (*196*), whereas the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is 2 ppm (*197*).

Tetrachloroethylene is a common organic solvent with relatively low oral toxicity in mice and rats, but it can affect the human nervous system by the inhalation route at relatively low exposure concentrations (Table 4). It is a mild eye irritant and a mild-to-severe skin irritant in rabbits (Table 4). Tetrachloroethylene is a proven animal carcinogen and a possible human carcinogen (Table 5) (*160*). It is genotoxic in numerous test systems (Table 5), is positive for reproductive toxicity in mice and rats for several end points, and is a possible human neurotoxicant under long-term, low-dose exposure conditions (*159,164*). The OSHA PEL for tetrachloroethylene is 100 ppm (670 mg/m^3) (*197*); the TLV is 25 ppm (170 mg/m^3) with a short-term exposure limit (STEL) of 100 ppm (685 mg/m^3) (*196*).

Hexachloroethane has relatively low oral toxicity in rats and guinea pigs [4–5 g/kg [*111*)] and low dermal toxicity in rabbits [32 g/kg (*111*)] (Table 4). It is a suspect human carcinogen based on carcinogenic activity in mice and rats (*167,171*) and has shown limited genotoxic activity (*167*) (Table 5). Hexachloroethane was not teratogenic in rats exposed orally (*111*), but chronic exposure of rats and mice caused renal toxicity (*170,171*). The OSHA PEL is 1 ppm (9.7 mg/m^3) (*197*), and the ACGIH TLV-TWA is 1 ppm (*167,196*).

1,2-Dichloroethane is another organic solvent for which many toxicity studies are available (Table 4). It is toxic by several routes of exposure including both oral and inhalation. Estimates of oral toxicity in terms of LD_{LO} values in humans range from 286 to 714 mg/kg. It is a mild skin irritant and a severe eye irritant in rabbits (Table 4). Like tetrachloroethylene and hexachloroethane, 1,2-dichloroethane is a known animal carcinogen and a likely human carcinogen (Table 5). It is genotoxic and has effects on a number of end points (Table 5). 1,2-Dichloroethane was negative for teratogenicity in two studies (*174,181*), negative for certain other reproductive toxicity end points (*174*), but caused embryonic growth retardation in rats (*181*). The OSHA PEL is 50 ppm with a 15-min STEL of 100 ppm (*197*), whereas the ACGIH TLV is 10 ppm (40 mg/m^3) (*167,196*).

1,1,2,2-Tetrachloroethane also is a halogenated solvent with numerous data for both acute and chronic toxicity (Tables 4 and 5). It is moderately toxic on acute exposure, with an oral LD_{50} value in rats of 250 mg/kg (*124*) and an inhalation LC_{50} value in mice of 4,500 mg/m^3 (*127*) (Table 4). 1,1,2,2-Tetrachloroethane is considered by the U.S. Environmental Ptoection Agency (EPA) to be a possible human carcinogen on the basis of tumor induction in male and female mice, although it was negative in male and female rats for carcinogenicity (*184*) (Table 5). It is mutagenic and shows other evidence of genotoxicity: it is positive for inducing DNA repair (*187*), SCE (*162*), and DNA damage (prophage lambda test in *Escherichia coli*) (*188*), and is positive in the replicative DNA synthesis test (*166*). No data relevant to reproductive toxicity were located. The OSHA PEL for tetrachloroethane is 5 ppm (35 mg/m^3) (*197*), whereas the ACGIH TLV-TWA is 1 ppm (6.9 mg/m^3) (*167,196*).

Ecotoxicology. The environmental toxicity of sulfur mustard was reviewed by Opresko et al. (*19*). The reviewed studies demonstrated that sulfur mustard is extremely toxic to all species, but its environmental action is limited by its low solubility. Results of these studies, involving a variety of aquatic organisms, showed that fish are the most sensitive species (compared with phytoplankton and higher aquatic plants). Mustard added to fish aquaria at 25°C formed globules on the bottom of the tanks, and amounts equivalent to 25–50 ppm were required for lethality in fish (*198*). For the three most sensitive species of fish, bluegill sunfish (*Lepomis macrochirus*), red-eared sunfish (*Lepomis microlophus*), and black bullheads (*Ameiurus melas*), the 30-day toxicity threshold was 2 mg/L.

We located few data on the toxicity of intermediate degradation products; however, several degradation products, including vinyl sulfoxide and 2-chloroethyl vinyl sulfoxide, have been tested as pesticides (*199,200*), which would indicate substantial toxicity to some species. The sulfur mustard–TDG–TDG aggregate was lethal to bluegill sunfish at ≥ 1,000 mg/L in 30-day tests (*198*). 1,4-Dithiane did not inhibit the growth of the plants *Brassica sativa* and *Medicago sativa*; furthermore, it was not toxic to gram-negative or gram-positive bacteria (*201*).

The metabolite TDG is practically nontoxic to aquatic organisms and terrestrial crops. At a concentration of 1,000 mg/L, TDG was not toxic to small bluegill sunfish within a 42-day observation period (*201*). TDG, applied by aerial application at 1 lb/acre, had no effect on several crop species including beans, oats, rice, soybeans, and radishes (*5*). Although the toxicity of H and HD probably precludes biodegradation (*5*), several strains of bacteria are capable of using TDG as their sole source of carbon for growth, indicating little toxicity (*29,52,53*). Also, following hot-water hydrolysis of sulfur mustard, presumably resulting in TDG and several thioethers, two different microtoxicologic tests detected no toxicity in the resulting medium (*53*).

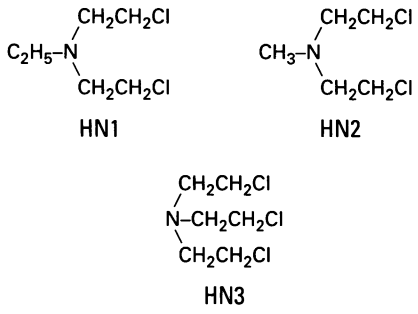
The generally low K_{ow} values (< 2) for mustard degradation products listed in Table 3 indicate a low potential to partition to the lipid phase in organisms and thus little potential to bioconcentrate.

Nitrogen Mustard Agents

The nitrogen mustards are not manufactured in significant commercial quantities in the United States. Although several of the nitrogen mustards have medicinal uses as antineoplastic agents (*12*), they were never stockpiled as part of the U.S. CW inventory. Because these agents are not a significant part of the U.S. CW agent inventory, they are not anticipated to be an environmental concern. We were able to locate little fate and toxicity data on nitrogen mustards. Because they are not very soluble in water, most research has involved the readily soluble hydrochloride compounds.

The three nitrogen mustards with greatest potential for warfare use are HN1, HN2, and HN3. These compounds are halogenated tertiary aliphatic amines. All three are colorless and odorless oily liquids when freshly distilled. Within days after distillation, HN3 takes on a yellow-to-brown color (*7*). Like all amines, the nitrogen mustards are bases and act as proton acceptors. Nitrogen mustards are unstable in the presence of light and heat and form dimers at temperatures above 50°C. Dimerization occurs even under ideal storage conditions and is accelerated in the presence of water (*6,7*). HN3 possesses

vesicant properties almost equal to those of HD; it is also the most stable in storage of the three nitrogen mustards (*11*).



Formation of degradation products. On the basis of chemical and physical properties such as volatility and susceptibility to hydrolysis (Table 1), HN3 is considered environmentally persistent, whereas HN1 and HN2 are considered moderately persistent. The major fate process in soil or water is expected to be hydrolysis, especially under weakly alkaline conditions.

The vapor pressure of all three nitrogen mustards is low, < 1 mmHg at 20–25°C. HN1 and HN2 have slightly higher vapor pressures than HN3. Because the volatility of HN3 is limited (approximately 100 mg/m^3 at 20°C), dangerous concentrations will not be found in the atmosphere (*7*). HN1 and HN2 are more volatile: 1,520 mg/m^3 at 20°C and 3,580 mg/m^3 at 25°C, respectively (*15*). The low values of 8.5×10^{-8} atm × m^3/mol and 3×10^{-7} atm × m^3/mol estimated for the Henry's Law constants of HN2 and HN3, respectively (*17,18*), indicate little to no volatilization from water and moist soil. Any HN3 in the atmosphere is predicted to react with photochemically produced hydroxyl radicals, resulting in an estimated half-life of 5 hr (*17,18*). Because they have chemical structures similar to HN3, any HN1 and HN2 in the atmosphere would also be photolytically degraded.

As noted, the nitrogen mustards are not very soluble in water; Franke (*7*) reported values of approximately 0.16 g/L for HN1 and HN3 and 12 g/L for HN2. In accordance with water solubility, hydrolysis of HN3 is slower than that of the sulfur mustards, but the hydrolysis reactions of HN1 and HN2 are probably more rapid. The mechanism of hydrolysis is similar for all three nitrogen mustards, with formation of a cyclic intermediate. For HN1, solubility is expected to increase with decreasing temperature; Epstein et al. (*35*) calculated a half-life of 12.5 days at 5°C for HN1 and all of its toxic hydrolysis products, including the intermediate chlorohydrin. The rate of hydrolysis in freshwater and seawater is expected to be similar. The Syracuse Research Corporation calculated a hydrolysis half-life of 11 hr at 25°C for HN2 (*17*). Hydrolysis is slower for HN3 but is estimated to be 90–95% complete with removal of all three chlorines after 24 hr (*18*).

Hydrolysis products were identified in several laboratory studies (Table 6). Epstein et al. (*35*) identified the final hydrolysis product of HN1 as bis(β-hydroxyethyl)amine or diethanolamine. Franke (*7*) identified *N*-methyl-2-hydroxy-2-chlorodiethyl ammonium chloride, a small amount of *N*-methylbis-(2-hydroxyethyl) ammonium chloride, and dimerization products as hydrolysis products of HN2 under laboratory conditions. The hydrolysis of HN3 is slower than that of the other two nitrogen mustards and also is complicated by formation of the reactive intermediates and dimerization products. In a 1% aqueous solution of HN3, bis(2-chloroethyl)-2-hydroxyethyl ammonium chloride and 2-chloroethyl-bis-(2-hydroxyethyl) ammonium chloride [along with a small amount of triethanol ammonium chloride (triethanolamine)] were identified after 20 and 72 hr, respectively. Much of the unhydrolyzed HN3 was in the form of the hydrochloride. Black and Read (*202*) listed triethanolamine, *N*-ethyldiethanolamine, and *N*-methyldiethanolamine as hydrolysis products of nitrogen mustards, presumably of HN3, HN1, and HN2, respectively.

The hydrolysis of HN3 involves successive displacement of the chlorides by hydroxy groups forming the three compounds listed in order in Table 6. The pathways for hydrolysis of HN1 and HN2 are similar with liberation of chloride and formation of the 1-methyl-1-(2-chloroethyl)-ethylenimonium ion. The onium cation then reacts with water to form the alcohol (chlorohydrin compound). The second carbon–chlorine bond hydrolyzes in a similar manner to form ethyldiethanolamine in the case of HN1 and methyldiethanolamine in the case of HN2 (*17*). Removal of the alkyl group results in diethanolamine. The ethylenimonium intermediates are highly reactive and can alkylate biologic macromolecules (*12*).

On the basis of K_{ow} values and using a regression-derived equation, the Syracuse Research Corporation (*17,18*) estimated K_{oc} values of 74 and 672 for HN2 and HN3, respectively. These values suggest high and low-to-medium mobility in soil for HN2 and HN3, respectively. The rapid hydrolysis of HN2 may preclude leaching through soil. No measured data were located.

No data on the biodegradation of nitrogen mustards were located. According to Morrill et al. (*44*), nitrogen mustards can theoretically be biodegraded by reductive dehalogenation and dehydrohalogenation mechanisms, but these processes would be very slow. HN1 and HN2 can be degraded through oxidative dealkylation (*N*-dealkylation for HN1 and *C*-dealkylation for HN2); the metabolites would possess vesicant properties. Yordy and Alexander (*203*) identified *N*-nitrosodiethanolamine as a metabolite of diethanolamine in natural waters and sewage.

We located further data on the fate of two hydrolysis products: diethanolamine (from HN1) and triethanolamine (from HN3). Both of these compounds have

Table 6. Hydrolysis products of nitrogen mustards.

Name/synonyms	Chemical formula	CAS no.
Ethylbis(2-chloroethyl)amine (HN1) degradation products		
N-Ethyldiethanolamine	$C_6H_{15}NO_2$	139-87-7
Diethanolamine	$C_4H_{11}NO_2$	111-42-2
2,2′-Iminodiethanol		
Bis(2-hydroxyethyl)amine		
Methylbis(2-chloroethyl)amine (HN2) degradation products		
N,N′-Dimethyl-*N,N′*bis(2-chloroethyl)piperazinium dichloride[a] (dimerization product)	$C_{10}H_{22}Cl_2N_2$•2HCl	63867-58-3
N-(2-Chloroethyl)-*N*-(2-hydroxyethyl)methylamine hydrochloride[b]	$C_5H_{12}NOCl$•HCl	63905-05-5
2,2′-(Methylimino)bis ethanol hydrochloride[c]	$C_5H_{13}NO_2$•HCl	54060-15-0
Tris(2-chloroethyl)amine (HN3) degradation products		
Bis(2-chloroethyl)-2-hydroxyethyl ammonium chloride[d]	$C_6H_{13}NOCl_2$•HCl	63978-53-0
2-Chloroethyl-bis(2-hydroxyethyl)ammonium chloride[e]	$C_6H_{14}NO_2Cl$•HCl	63978-75-6
Triethanol ammonium chloride[f]	$C_6H_{15}NO_3$•HCl	637-39-8
Triethanolamine hydrochloride		
Tris(2-hydroxyethyl)ammonium chloride		

Data from Franke (*7*), Epstein et al. (*35*), and Black and Read (*56*).
[a]The nonhydrochloride is *N,N′*-dimethyl-*N,N′*bis(2-chloroethyl) piperazinium ($C_{10}H_{22}Cl_2N_2$; CAS no. 51822-58-3). [b]Product was present in solution as hydrochloride (*7*); the nonhydrochloride compound is 2-(2-chloroethyl)methylamino ethanol ($C_5H_{12}NOCl$; CAS no. 51822-57-2). [c]Product was present in solution as hydrochloride (*7*); the nonhydrochloride compound is *N*-methyldiethanolamine ($C_5H_{13}NO_2$; CAS no. 105-59-9). [d]Product was present in solution as hydrochloride (*7*); the nonhydrochloride compound is ethanol mustard ($C_6H_{13}NOCl_2$; CAS no. 7747-69-5). [e]Product was present in solution as hydrochloride (*7*); the nonhydrochloride compound was not identified. [f]Product was present in solution as hydrochloride (*7*); the nonhydrochloride compound is triethanolamine ($C_6H_{15}NO_3$; CAS no. 102-71-6).

industrial uses (*14*), and their presence in the environment is not unique to CW agent contamination. Diethanolamine released to soil or water is expected to biodegrade with a half-life of a few days to weeks depending on microbial acclimation. Leaching through soil is expected, as the compound is miscible with water; however, the protonated compound may adsorb to humic material in soil and water. Based on a vapor pressure of 1.4×10^{-4} mmHg and an estimated Henry's Law constant of 3.9×10^{-11} atm × m^3/mol, volatilization from soil and water, respectively, are not important fate mechanisms. The half-life of diethanolamine vapor in the atmosphere has been estimated at 4 hr (*204*), and complete mineralization of diethanolamine in sewage has been reported (*204,205*). Similar fate data were presented for triethanolamine (*206*).

Decontamination. No specific information on decontamination was located. Franke (*7*) noted that HN3 is unstable and that hydrolysis in solution is accelerated as the pH and temperature increase. Franke (*7*) listed numerous reactions of HN3 with other chemicals, including reaction with alcoholic sodium sulfide, which results in detoxification. A 5% hydrochloric or hydrosulfuric acid solution was recommended for detoxification of machinery, as the resulting salt is water soluble. However, treatment with HCl results in tris(2-chloroethyl) ammonium chloride, which is just as toxic as the free amine. HN3 is unreactive with most oxidative detoxification chemicals. HN1 and HN2 are chemically similar to HN3 and should react similarly.

Acute and chronic mammalian toxicity. The nitrogen mustards are highly toxic vesicant agents with strong alkylating activity and significant systemic toxicity in addition to their blistering capability.

Tables 7 and 8 list toxicity information for the HN degradation products. *N*-ethyldiethanolamine and diethanolamine are the degradation products of HN1. *N*-ethyldiethanolamine produces severe eye irritation in rabbits but only mild skin irritation; it exhibits low oral toxicity in rats (Table 7). No chronic toxicity information was found for this substance. Diethanolamine is a severe eye and skin irritant (*157*); it is moderately toxic in several animal species by oral exposure and very mildly toxic by the dermal route (Table 7). Although diethanolamine has consistently given negative results in tests for mutagenicity and cytogenicity (Table 8) (*157*), it has demonstrated evidence of male rat reproductive toxicity (*220*) and clear evidence of carcinogenicity in male and female mice after a 2-year dermal exposure (*218*). The OSHA PEL for diethanolamine was 3 ppm until vacated in 1992 by a court decision (*157*); the TLV-TWA has been revised downward to 0.46 ppm (2 mg/m^3) (*167,196*).

Table 7 lists acute toxicity data for two HN2 hydrolysis products, *N*-methyl-2-hydroxy-2-chloro diethyl ammonium chloride and *N*-methyldiethanolamine. The former is highly toxic by the oral and sc routes in rats and mice (*7,66*). *N*-methyldiethanolamine is mildly toxic by the oral and dermal routes (*70*) and generates mild skin irritation (*211*). It does not produce mutations in *Salmonella* (*222*) or inhibit mitosis in mouse vaginal epithelium *in vivo* (*211*), and it does not cross-react with HN2 for delayed hypersensitivity in humans (*211*). The salts of two other HN2 hydrolysis products were also tested for mitotic inhibition and human hypersensitivity cross-reaction with HN2. 2-(2-Chloroethyl) methylamino ethanol hydrochloride was positive in both regards (*211*), whereas *N,N'*-dimethyl-*N,N'*bis(2- chloroethyl) piperazinium was negative in both tests (*211*) (Table 8).

Table 7. Effects of acute exposure to HN1, HN2, and HN3 degradation products.[a]

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	Other effects
HN1 hydrolysis		
N-Ethyldiethanolamine ($C_6H_{15}NO_2$; 139-87-7)	Rat: oral, 4,570 mg/kg (*70*)	Rabbit: skin, 10 mg/24 hr open, mild irritation (*70*) Rabbit: skin, 500 mg/24 hr, mild irritation (*110*) Rabbit: eye, 750 µg open, severe irritation (*70*)
Diethanolamine ($C_4H_{11}NO_2$; 111-42-2)	Rat: oral, 710 mg/kg (*89*) Mouse: oral, 3,300 mg/kg (*208*) Rabbit: oral, 2,200 mg/kg (*209*) Guinea pig: oral, 2 g/kg (*157*) Rabbit: dermal, 11.9 mL/kg (*205*) Guinea pig: dermal, 11,900 µL/kg (*210*)	Rabbit: skin, 50 mg open, mild irritation (*207*) Rabbit: skin, 500 mg/24 hr mild irritation (*110*) Rabbit: eye, 5,500 mg, severe irritation (*64*) Rabbit: eye, 750 µg/24 hr, severe irritation (*110*)
HN2 hydrolysis		
N-Methyl-2-hydroxy-2-chloro-diethyl ammonium chloride ($C_5H_{13}NOCl{\bullet}HCl$; 63905-05-5)	Rat: oral, 80 mg/kg (*66*) Mouse: oral, 25 mg/kg (*66*) Rat: sc, 20 mg/kg (*66*) Mouse: sc, 16 mg/kg (*7*)	
2-(2-Chloroethyl) methylamino ethanol hydrochloride ($C_5H_{13}NOCl$; 51822-57-2)		Human: skin, delayed hypersensitivity, positive for HN2 cross-reaction (*211*)
N-Methyldiethanolamine ($C_5H_{13}NO_2$; 105-59-9)	Rat: oral, 4,780 mg/kg (*70*) Rabbit: dermal, 5,990 µL/kg (*70*)	Human: skin, delayed hypersensitivity, negative for HN2 cross-reaction (*211*) Rabbit: skin, 10 mg/24 hr open, mild (*70*) Rabbit: skin, 502 mg, open, mild (*70*) Rabbit: eye, 20 mg open, effect not specified (*70*)
N,N'-Dimethyl-*N,N'*bis (2-chloroethyl) piperazinium ($C_{10}H_{22}Cl_2N_2$; 51822-58-3)		Human: skin, delayed hypersensitivity, negative for HN2 cross-reaction (*211*)
HN3 hydrolysis		
Bis(2-chloroethyl)-2-hydroxyethyl ammonium chloride ($C_6H_{13}NOCl_2{\bullet}HCl$; 63978-53-0)	Mouse: ip, 1,500 µg/kg (*66*)	
2-Chloroethyl-bis(2-hydroxyethyl) ammonium chloride ($C_6H_{14}NOCl_2{\bullet}HCl$; 63978-75-6	Mouse: ip, 16 mg/kg (*66*) Mouse: sc, 5 mg/kg (*66*)	
Triethanolamine ($C_6H_{15}NO_3$; 102-71-6)	Rat: oral, 4,920 µL/kg (*212*) Mouse: oral, 5,846 mg/kg (*214*) Rabbit: oral, 2,200 mg/kg (*127*) Guinea pig: oral, 2,200 mg/kg (*127*) Rat: dermal, > 16 mL/kg (*212*) Rabbit: dermal, > 20 mL/kg (*217*)	Human: skin, 15 mg/3 days, mild (*213*) Rabbit: skin, 560 mg/24 hr, mild (*215*) Rabbit: eye, 20 mg, severe (*64*) Rabbit: eye, 10 mg, mild (*216*) Rabbit: eye, negligible to moderate irritation (*194*)

Abbreviations: HN1, ethylbis(2-chloroethyl)amine; HN2, methylbis(2-chloroethyl)amine; HN3, tris(2-chloroethyl)amine; ip, intraperitoneal; LC_{50}, median lethal concentration; LD_{50}, median lethal dose; sc, subcutaneous.
[a]No effects were found in the literature for lowest lethal dose (lowest lethal concentration).

Except for triethanolamine, toxicity data are sparse for the hydrolysis products of HN3. The available data suggest high acute toxicity for both bis(2-chloroethyl)-2-hydroxyethyl ammonium chloride and 2-chloroethyl-bis(2-hydroxyethyl) ammonium chloride (Table 7). The mouse sc LD_{50} value for the latter compound is very close to that for HN3 [2 mg/kg (*228*)]. Triethanolamine, however, shows very low acute toxicity by the oral and dermal routes (Table 7). It is a mild skin irritant; eye irritation data from rabbits are mixed (mild to severe; Table 7). Triethanolamine has caused various skin effects upon occupational exposure, including irritation, contact dermatitis, allergic contact dermatitis, eczema, and erythematous vesicular lesions (*157*). It has given negative results for various genotoxicity end points (Table 8) (*157*) and for effects on sperm morphology in rodents (*223*). In 2-year dermal carcinogenesis testing, triethanolamine gave equivocal results in male rats and no evidence in female rats (*223*). It is embryotoxic in chicks (*225*). It did not produce skin sensitization in mice (*226*), but upon chronic exposure it did cause skin hyperplasia and inflammation in mice and rats and skin ulceration in rats (*223*). The TLV-TWA for triethanolamine is 5 mg/m^3 (*196*). No OSHA PEL exists for triethanolamine.

Ecotoxicity. We located data on the acute aquatic toxicity of three degradation products: *N*-ethyldiethanolamine, diethanolamine, and triethanolamine (Table 9). The data indicate that these hydrolysis products are of low-to-moderate toxicity to aquatic organisms. No data on the acute toxicity of the parent compounds were located for comparison purposes. In 30-day tests, thresholds for lethality for fish (black bullheads) were 25 mg/L for HN1; 10 mg/L for HN2; and 8 mg/L for HN3 (*198*). When introduction of the fish into the tanks containing 25 mg/L HN3 was delayed for 12 hr, all fish survived, indicating a loss of toxicity, presumably through hydrolysis. According to Buswell et al. (*198*), the nitrogen mustards were less toxic than sulfur mustard to phytoplankton and higher aquatic plants. Bioconcentration factors of < 1 for both diethanolamine and triethanolamine and their high water solubility indicate that neither compound will bioconcentrate in aquatic organisms (*204,206*). No data were located on toxicity of the degradation products to terrestrial plants or wildlife.

Lewisite

Lewisite [dichloro(2-chlorovinyl)arsine; Cl-CH = CH-$AsCl_2$] is an organic arsenical with vesicant properties. Purified Lewisite is a colorless, oily liquid with very little odor, whereas the synthesized chemical agent is an amber-to-dark brown liquid with a geranium-like odor (*10,15*). The synthesized agent is composed of *cis* and *trans* isomers in the ratio of 10:90 and several impurities including bis(2-chlorovinyl)chloroarsine, tris(2-chlorovinyl)arsine, and arsenic trichloride (*5,10*). The chemical and physical properties of the two isomers are similar. Because the vinyl double bond and the dichloroarsine group ($AsCl_2$) are unstable, stabilizers are normally added to prevent decomposition (*27*).

Lewisite, like GA, has been produced in limited quantity and is stored as part of the unitary stockpile only at Deseret Chemical Depot, formerly part of Tooele Army Depot (*229*). Small amounts of Lewisite are present as nonstockpile material (cartridges or projectiles) at several other military sites including Pine Bluff Arsenal, Arkansas, and Dugway Proving Ground, Utah (*25*). It is also present in chloroform solution in glass ampule war gas ID sets used for training purposes and found in several locations. Lewisite is thought to be present at another six nonstockpile sites in the United States (*230,231*).

Formation of degradation products. Lewisite is considered nonvolatile. However, with a vapor pressure of 0.58 mmHg at 25°C, Lewisite is more volatile than sulfur mustard agents and is used as a moderate

Table 8. Carcinogenicity, genotoxicity, reproductive toxicity, and systemic effects of chronic exposure to HN1, HN2, and HN3 degradation products.

Degradation product (formula; CAS no.)	Carcinogenicity	Genetic effects	Reproductive effects	Systemic effects
HN1 hydrolysis				
Diethanolamine ($C_4H_{11}NO_2$; 111-42-2)	Rat: dermal, negative Mouse: dermal, male and female, positive (*218*)	Mutagenicity: Ames test, negative (*169*); mouse lymphoma, negative (*218*) Cytogenetic effects: chromosome aberrations, SCE, negative (*221*) Mouse micronucleus induction: negative (*218*)	Rat: oral, seminiferous tubule degeneration, 14 days and 13 weeks (*219*) Rat: oral, 13 weeks, decreased sperm count and motility, changes in testis weight (*219,220*)	Rat: oral and dermal, microcytic anemia, decreased renal function, demyelinization of brainstem and spinal cord (*220*) Rat: dermal, ulcerative skin lesions (*220*) Mouse: oral, increased liver weight, nephropathy and tubular necrosis, cardiac myocyte degeneration, hepatocellular necrosis (*220*) Mouse: dermal, skin lesions, liver, kidney and cardiac myocyte degeneration (*220*)
HN2 hydrolysis				
2-(2-Chloroethyl) methylamino ethanol hydrochloride ($C_5H_{13}NOCl$; 51822-57-2)		Mouse: intravaginal, mitotic inhibition, positive (*211*)		
N-methyldiethanolamine ($C_5H_{13}NO_2$; 105-59-9)		Mutagenesis: Ames test, negative (*222*) Mouse: intravaginal, mitotic inhibition, negative (*211*)		
N,N'-dimethyl-*N,N'*bis (2-chloroethyl) piperazinium ($C_{10}H_{22}Cl_2N_2$; 51822-58-3)		Mouse: intravaginal, mitotic inhibition, negative (*211*)		
HN3 hydrolysis				
Triethanolamine ($C_6H_{15}NO_3$; 102-71-6)	Carcinogenesis: equivocal in male rats; no evidence in female rats (*223*)	Mutagenesis: Ames test, negative (*224*) Mutagenesis: *Drosophila*, negative (*227*) Cytogenicity: chromosome aberrations, SCE, negative (*162*) Mouse: micronucleus test, negative (*223*)	Chick: embryotoxic (*225*) Rat and mouse: sperm morphology effects, negative (*223*)	Mouse: skin sensitization, negative (*226*) Rat: skin hyperplasia, inflammation, ulceration (*223*) Mouse: skin hyperplasia and inflammation (*223*) Mouse: altered liver cells (*223*)

Abbreviations: HN1, ethylbis(2-chloroethyl)amine; HN2, methylbis(2-chloroethyl)amine; HN3, tris(2-chloroethyl)amine; SCE, sister chromatid exchange.

irritant vapor over greater distances than sulfur mustard (*2*). Although no data were located on its fate in the atmosphere, its UV absorption spectrum at 200–350 nm is greater than that of other nonstockpile chemical agents (*32*) and indicates that some photodegradation may take place. Hydrolysis may also occur in the gas phase (*27*).

Although Lewisite is only slightly soluble in water [0.5 g/L (*5*)], hydrolysis is rapid and results in the formation of the water-soluble dihydroxy arsine (2-chlorovinyl arsonous acid) (Table 10). Although most reviews state that the hydrolysis is complex, with a number of reversible reactions resulting in the formation of Lewisite oxide (*5,9,27,232*), the equilibrium between Lewisite, Lewisite oxide, and 2-chlorovinyl arsonous acid is not a true equilibrium because no detectable Lewisite or Lewisite oxide remains and the solution becomes 100% 2-chlorovinyl arsonous acid (*233*):

$$\text{Cl–CH=CH–AsCl}_2 + 2\text{H}_2\text{O} \rightleftarrows \text{Cl–CH=CH–As(OH)}_2 + 2\text{HCl}$$

Formation of Lewisite oxide (chlorovinyl arsenous oxide) and polymerized Lewisite oxide is essentially a dehydration reaction:

$$\text{Cl–CH=CH–As(OH)}_2 \rightleftarrows \text{H}_2\text{O}\uparrow + \text{Cl–CH=CH–AsO} + (\text{Cl–CH=CH–AsO})_n$$

Once formed, Lewisite oxide and polymerized Lewisite oxide are relatively insoluble in water. Once dry, the oxide will probably not readily redissolve or form the acid in the environment.

In basic solution, the *trans*-Lewisite isomer is cleaved by the hydroxyl ion to give acetylene and sodium arsenite; this occurs even at low temperatures (*5,9*). *cis*-Lewisite must be heated to over 40°C to react with NaOH to yield vinyl chloride, sodium arsenite, and acetylene (*5*). In aqueous solution, the *cis* isomer undergoes a photoconversion to the *trans* isomer (*5*). In water and in the presence of oxidizers naturally present in the environment, the toxic trivalent arsenic of Lewisite oxide is oxidized to the less toxic pentavalent arsenic (*232*). Regardless of the degradation pathway, arsenical compounds will ultimately be formed.

A Henry's Law constant of 3.2×10^{-4} atm $\times$ m^3/mol for Lewisite indicates the potential for significant volatilization from water. However, the rapid rate of hydrolysis may reduce the significance of this fate pathway.

Although the low water solubility of Lewisite indicates intermediate persistence in moist soil (*2,10*), Lewisite applied to soil may rapidly volatilize and/or be converted to Lewisite oxide through exposure to soil moisture followed by drying (*5*). According to Cooper (*234*), Lewisite is easily hydrolyzed in soil, and minerals present in soil would increase the degradation rate. Furthermore, alkaline soils would neutralize Lewisite. In soil, both Lewisite and Lewisite oxide may be slowly oxidized to 2-chlorovinyl arsonic acid (*5*). Suggested pathways of microbial degradation in soil include epoxidation of the C=C bond and reductive dehalogenation and dehydrohalogenation (*44*). The latter pathways result in toxic metabolites because of the epoxy bond and arsine group.

Of the Lewisite degradation products, 2-chlorovinyl arsonous acid is water soluble and nonvolatile (*235*). No data were located on the presence or environmental persistence of this compound at contaminated sites. The log K_{ow} of 2-chlorovinyl arsonous acid is -0.07 (*233*). Also, little is known of the stability of Lewisite oxide in the environment. As noted above, the possibility exists for oxidation of the oxide in soil to 2-chlorovinyl arsonic acid. Conversion to inorganic arsenic in soil may also take place (*5*). According to Rosenblatt et al. (*5*) the impurity, bis(2-chlorovinyl)arsine, is less volatile than Lewisite.

Decontamination. Lewisite is readily oxidized to 2-chlorovinyl arsonic acid by a variety of oxidants including hypochlorous acid, hydrogen peroxide, chloramines, and iodine; seawater also oxidizes Lewisite (*5*). As noted above, *trans*-Lewisite is cleaved by alkalies to give acetylene, arsonite (AsO_3^{3-}), $3Cl^-$, and water. This reaction is rapid and occurs even at low temperatures (*5,57*). *cis*-Lewisite must be heated to over 40°C to react with NaOH to yield vinyl chloride, sodium arsenite, and acetylene (*5*). Anhydrous Lewisite interacts with chlorine to yield arsenic trichloride and dichloroethylene (*10*).

Acute and chronic mammalian toxicity. Lewisite has significant systemic toxicity in addition to its blister-forming effects on skin and its irritative effects on the eyes and respiratory tract (*2*).

Under acidic conditions, Lewisite forms the hydrolysis products 2-chlorovinyl arsonous acid and 2-chlorovinyl arsenous oxide (Lewisite oxide). Because of the rapid conversion of Lewisite to 2-chlorovinyl arsonous acid upon contact with the human body, the

Table 9. Toxicity of nitrogen mustard degradation products to aquatic species.

Chemical	Test species	Test type	Concentration (mg/L)
HN1 degradation products			
N-ethyldiethanolamine	Fish (*Semolitus atromaculatus*)	24-hr LC_{50}	160–200
Diethanolamine	Algae (*Scendesmus subspicatus*)	72-hr EC_{50}	75
	Crustacean (*Daphnia magna*)	48-hr LC_{50}	55, 110
	Fish (*Pimephales promelas*)	96-hr LC_{50}	1,664
HN3 degradation products			
Triethanolamine	Algae (*Sc. subspicatus*)	48-hr EC_{50}	62, 110
	Crustacean (*D. magna*)	24-hr LC_{50}	1,360–2,038
	Fish (*Carassius auratus*)	24-hr LC_{50}	> 5,000

Abbreviations: EC_{50}, median effective concentration; HN1, ethylbis(2-chloroethyl)amine; HN3, tris(2-chloroethyl)amine; LC_{50}, median lethal concentration. Where multiple species were tested, representative data are listed. Data from Verschueren (*205*).

Table 10. Degradation products and impurities of Lewisite.

Name/synonyms	Formula	CAS no.	Source
2-Chlorovinyl arsonous acid (CVA) 2-Chlorovinyl arsenous acid 2-Chloroethenyl arsonous acid Dihydroxy(2-chlorovinyl)arsine 2-Chloroethenyl dihydroxyarsine	$C_2H_4AsClO_2$	85090-33-1	Hydrolysis of Lewisite
2-Chlorovinyl arsenous oxide 2-Chlorovinyl arsenic oxide 2-Chlorovinyl arsine oxide 2-Chloroethenyl arsinic oxide Lewisite oxide	C_2H_2AsClO	3088-37-7	Hydrolysis or dehydration of 2-chlorovinyl arsonous acid
Lewisite oxide polymer	$(C_2H_2AsClO)_n$	Not available	Polymer of Lewisite oxide
2-Chlorovinyl arsonic acid 2-Chloroethenyl arsonic acid	$C_2H_4AsClO_3$	64038-44-4	Oxidation of Lewisite oxide
Bis(2-chlorovinyl)chloroarsine Bis(2-chloroetheynl)dichloroarsine Lewisite 2	$C_4H_4AsCl_3$	40334-69-8 50361-06-3	Impurity
Tris(2-chlorovinyl)arsine Tris(2-chloroethenyl)arsine Lewisite 3	$C_6H_6AsCl_3$	40334-70-1	Impurity
Arsenic trichloride	$AsCl_3$	7784-34-1	Impurity

Data from Rosenblatt et al. (*5*), Franke (*7*), Clark (*9*), Goldman and Dacre (*10*), and Sanches et al. (*34*).

toxic properties of Lewisite may actually be those of 2-chlorovinyl arsonous acid (*235*). No further details on the toxicity of 2-chlorovinyl arsonous acid were found. The U.S. Army reported that Lewisite oxide has vesicant properties, but provided no details regarding its potency (*228*). Its acute toxicity to the mouse by the subcutaneous route is quite high, judging from the one available data point, an LD_{LO} of 5 mg/kg (*75*) (Table 11). We found no equivalent mouse data for Lewisite for purposes of comparing lethalities (*228*). In the absence of data, Bausum et al. (*190*) considered using the proposed RfD developed for Lewisite of 0.1 µg/kg/day (*237*) for Lewisite oxide. The National Academy of Sciences Committee on Toxicology, Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents, is considering this value and the existing RfD for inorganic arsenic, 0.3 µg/kg/day (*238*), as the RfD for Lewisite (*19*). Bausum et al. (*190*) recommended that the RfD for inorganic arsenic of 0.3 µg/kg/day be used for Lewisite oxide.

We located only one toxicity value for the oxidation product 2-chlorovinyl arsonic acid. The rat oral LD_{LO} of 50 mg/kg suggests moderately high acute toxicity (Table 11). According to Rosenblatt et al. (*5*), the impurity, bis(2-chlorovinyl)arsine, has a toxicity comparable to that of Lewisite.

No chronic toxicity data for Lewisite degradation products were located. It is unlikely that these compounds exhibit carcinogenicity, although there are no data specific to them. The Centers for Disease Control (*239*) stated that "some evidence suggests that Lewisite might also be a carcinogen." However, Goldman and Dacre (*10*) reviewed the potential carcinogenicity of organic arsenicals including Lewisite and contended that there is no persuasive evidence for such activity.

No OSHA or ACGIH values are available for 2-chlorovinyl arsenous oxide and 2-chlorovinyl arsonous acid. However, the OSHA PEL-TWA of 0.5 mg (As)/m^3 for organic arsenic compounds (*197*) can be applied to these compounds (*240*). No ACGIH TLV is listed for organic arsenic compounds (*196*).

Depending on environmental conditions, various inorganic arsenic compounds can be formed in the course of complete Lewisite mineralization; inorganic arsenic compounds are found in areas of past Lewisite releases, although the limited quantity of Lewisite present in the United States suggests limited areas of risk. Aside from its natural presence, arsenic may also be present in the environment as a result of past use of arsenical-containing herbicides such as cacodylic acid. As noted, the RfD for inorganic arsenic is 0.3 µg/kg/day (*238*). The carcinogenicity of inorganic arsenic compounds potentially formed during the degradation of Lewisite is relevant to worker safety. The oral and inhalation slope factors are 1.5 and 50 per mg/kg/day, and the drinking water unit risk is 0.00005/µg/L (*238*).

Ecotoxicity. Data on Lewisite are limited to a few historical reports. In 30-day tests, the thresholds for lethality for several aquatic organisms were 0.2 mg/L (small black bullheads), 0.5 mg/L (bluegill sunfish), < 2.0 mg/L (largemouth bass), and 0.5 mg/L (tadpoles) (*198*). In Lewisite solutions allowed to stand for 30 or 50 days, there was an increase in the survival rate of tested organisms (*241*), indicating a lower toxicity for the hydrolysis/oxidation products. In another study, sunfish exposed to 6.5 mg/L Lewisite for 24 hr showed signs of stress, but there were no deaths (*242*). No further details were available. Buswell et al. (*198*) compared the toxicity of Lewisite to that of arsenite ($NaAsO_2$) and found that the 30-day lethality threshold of arsenite for black bullheads was much greater (25 mg/L).

Buswell et al. (*198*) tested the toxicity of Lewisite in a variety of phytoplankton and aquatic plants (water milfoil, parrot's feather, and water crowfoot) in static 30-day tests at concentrations of 5 and 50 mg/L. At 5 mg/L, Lewisite inhibited the growth of the phytoplankton, and the water milfoil and water crowfoot died; at 50 mg/L, all plants died (*198*). Lewisite vapor is extremely phytotoxic and has been implicated in the death of vegetation in Lewisite shell target areas (*243*).

Few data were located on the ecotoxicity of degradation products. 2-Chlorovinyl arsonic acid was considerably less toxic to aquatic organisms than Lewisite, with only a slight toxic effect (not described) at 200 ppm (*241*). Hydrolysis of Lewisite results in arsenical compounds that persist in the environment; arsenic bioaccumulates through food chains (*244*), whereas Lewisite does not (*5*).

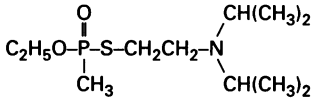
Table 11. Effects of acute exposure to Lewisite degradation products.

Degradation product (formula; CAS no.)	LD_{50}	LD_{LO}	Other effects
Chlorovinyl arsenous oxide (C_2H_4AsClO; 3088-37-7) (Lewisite oxide)	Mouse: subcutaneous, 5 mg/kg (*75*)		Irritant, vesicant (*229*)
2-Chlorovinyl arsonic acid ($C_2H_4AsClO_3$; 64038-44-4)		Rat: oral, 50 mg/kg (*236*)	

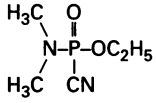
Abbreviations: LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose.

Nerve Agents

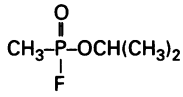
The nerve agents are alkylphosphonic acid esters. They are generally divided into V agents, primarily VX, and G agents, principally GA, GB, and GD. V agents such as VX contain a sulfur and are alkylphosphonothiolates. GA contains a cyanide group; GB and GD, which contain a fluorine substituent group, are methylphosphonofluoridate esters. These nerve agents contain a C–P bond that is almost unique, e.g., it is not found in organophosphate pesticides; the C–P bond is very resistant to hydrolysis. The chemical names, CAS No, and chemical and physical properties of the nerve agents are listed in Table 1.



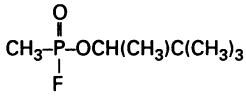
VX



GA



GB



GD

All of the nerve agents are viscous liquids; however, the V agents tend to be persistent on surfaces, whereas the G agents are volatile and present a vapor hazard. The agents also differ in water solubility, with GA and GB being miscible with water and VX and GD being less soluble. Hydrolysis rates of the nerve agents also differ, with the slowest being VX. Under ideal storage conditions, GA and GB are fairly stable when stored in steel containers; GD is less stable than GA and GB. VX is considered relatively stable at room temperature (*11*).

VX

VX is present in missiles and projectiles at seven army depots or arsenals in the United States and is stored in ton containers at Tooele Army Depot, Johnston Island in the Pacific Ocean, and the Newport Chemical Activity in Newport, Indiana (*25,245*). VX is also present at eight nonstockpile sites in six

states (*230,231*). VX is usually formulated with 1–3% of the stabilizers diisopropyl carbodiimide or dicyclohexyl carbodiimide to protect it against decomposition by trace amounts of water. A combination of methods is usually required to characterize the degradation products of VX; these methods include gas or liquid chromatography combined with mass spectrometry and nuclear magnetic resonance spectroscopy.

Formation of degradation products. Agent VX is a persistent, odorless, amber-colored liquid. VX is less volatile (10.5 mg/m^3 at 25°C) than the G agents and does not evaporate readily. A Henry's Law constant of

Table 12. Degradation products, impurities, and stabilizers of *O*-ethyl-*S*-[2-(diisopropylamino)ethyl]methylphosphonothioate (VX).

Name/synonyms	Formula	CAS no.	Source
Ethyl methylphosphonic acid (EMPA) Ethyl hydrogen methylphosphonate	$C_3H_9O_3P$	1832-53-7	Hydrolysis of VX
Diisopropyl ethyl mercaptoamine Diisopropylamino ethyl mercaptan (DESH, DIAEM) Diisopropylaminoethyl thiol 2-(Diisopropylamino) ethane thiol	$C_8H_{19}NS$	5842-07-9	Hydrolysis of VX
S-(2-Diisopropylaminoethyl) methylphosphonothioic acid *S*-(2-Diisopropylaminoethyl) methylphosphonothioate Diisopropylaminoethyl methyl thiolophosphonate EA 2192	$C_9H_{22}NO_2PS$	73207-98-4	Hydrolysis of VX
Bis(2-diisopropylaminoethyl) sulfide ([DE$_2$]S) *N,N'*-Thiodi-2,1-ethanediyl)bis(*N*-(1-methylethyl)-2-propanamine VX sulfide	$C_{16}H_{36}N_2S$	110501-56-9	Reaction of DESH with ethyleneimmonium ion
Bis(2-diisopropylaminoethyl) disulfide ([DES]$_2$) *N,N'*(Dithio-2,1-ethanediyl)bis(*N*-(1-methylethyl)-2-propanamine VX disulfide EA 4196	$C_{16}H_{36}N_2S_2$	65332-44-7	Dimerization of DESH Air oxidation of DESH
Ethyl methylphosphonothioic acid *O*-Ethyl methylphosphonothioate *O*-Ethyl methylthiophosphonate	$C_3H_9O_2PS$	18005-40-8	Hydrolysis of VX, VX precursor for some processes
2-Diisopropylaminoethanol *N,N*-Diisopropylamino ethanol	$C_8H_{19}NO$	96-80-0	Hydrolysis of VX
Methylphosphonic acid (MPA)	CH_5O_3P	993-13-5	Hydrolysis of EMPA
Bis[*S,S*-(2-diisopropylaminoethyl)]methylphosphonodithiolate "Bis" *S,S*-Bis{2-[bis(1-methylethyl)amino]ethyl}methylphosphono dithioic acid	$C_{17}H_{39}N_2OPS_2$	169493-13-4	Impurity formed during manufacture
Diisopropylaminoethyl sulfide	$C_8H_{19}NS$	NA	Present in ton containers
2-(Diisopropylamino) ethyl ethyl sulfide	$C_{10}H_{23}NS$	NA	Present in ton containers
Diethyl methylphosphonate *O,O*-Diethyl methylphosphonate	$C_5H_{13}O_3P$	683-08-9	Present in ton containers, degradation product and impurity
1-(2-Chloroethyl)-1,4 dithianium chloride[a] 1-(2-Chloroethyl)-1-thiona-4-thiane chloride Q-Sulfonium	$C_6H_{12}ClS_2{\bullet}Cl$	30843-67-5	Present in ton containers
1,2-Bis(ethyl methylphosphonothiolo) ethane	$C_8H_{18}O_4P_2S_2$	NA	Present in ton containers
O-(2-Diisopropylaminoethyl) *O'*-ethyl methylphosphonate 2-[Bis(1-methylethyl)amino]ethyl methylphosphonic acid	$C_{11}H_{26}NO_3P$	71840-26-1	Present in ton containers
O-Ethyl *S*-2-(diisopropylamino)ethyl methylphosphonothioate	$C_{11}H_{26}NO_2PS$	50782-69-9	Present in ton containers Present in stored glass container
O,O-Diethyl dimethylpyrophosphonothioate	NA	NA	Present in ton containers
O,O-Diethyl methylphosphonothioate	$C_5H_{13}O_2PS$	6996-81-2	Present in ton containers
O-Ethyl methylethylphosphinate	NA	NA	Present in ton containers
Diethyl dimethyl pyrophosphonate (pyro) Diethyl dimethyldiphosphonate	$C_6H_{16}O_5P_2$	32288-17-8	Impurity, anhydride of EMPA, present in ton containers
O,S-Diethyl methylphosphonothioate	$C_5H_{13}O_2PS$	2511-10-6	Impurity, present in ton containers
N,N-Diisopropylmethylamine	$C_7H_{17}N$	10342-97-9	Present in ton containers
N,N-Diisopropylethylamine	$C_8H_{19}N$	7087-68-5	Present in ton containers
2-Diisopropylamino ethyl vinyl sulfide	NA	NA	Impurity, present in ton containers
O,O'-Diethyl *P,P'*dimethyldiphosphonothioate	$C_6H_{14}O_4P_2S$	NA	Impurity, present in ton containers
N-Chloroisopropylamine	C_3H_8ClN	26245-56-7	Reaction with hypochlorite
N-Chlorodiisopropylamine	$C_6H_{14}ClN$	24948-81-0	Oxidation with hypochlorite (supertropical bleach)
Diisopropylamine	$C_6H_{15}N$	108-18-9	Present in ton containers, reaction with hypochlorite
Diisopropyltaurine	$C_8H_{19}NO_3S$	66263-86-3	Reaction with chlorine gas, oxidation with Oxone, decontamination with Fichlor[b]
Diisopropyl carbodiimide	$C_7H_{14}N_2$	693-13-0	Stabilizer
Dicyclohexyl carbodiimide *N,N'*-Methanetetraylbiscyclohexaneamine	$C_{13}H_{22}N_2$	538-75-0	Stabilizer
1,3-Diisopropylurea *N,N'*-Diisopropylurea *N,N'*Bis-(1-methylethyl) urea	$C_7H_{16}N_2O$	4128-37-4	Hydrolysis of diisopropyl carbodiimide
N,N'-Dicyclohexylurea	$C_{13}H_{24}N_2O$	2387-23-7	Hydrolysis of dicyclohexyl carbodiimide
1,9-Bis(diisopropyl amino)-3,4,7-trithianonane	$C_{18}H_40N_2S_3$	110501-59-2	Present in stored glass containers Supercritical water oxidation of VX
Mono (2-ethylhexyl) ester hexanedioic acid	$C_{14}H_{26}O_4$	4337-65-9	Supercritical water oxidation of VX

NA, not available. Data from Clark (*9*), Rosenblatt et al. (*13*), the National Research Council (*21*), Amr et al. (*23*), MacNaughton and Brewer (*27*), Kingery and Allen (*28*), Epstein et al. (*248*), Rohrbaugh (*249*), D'Agostino et al. (*250*).

[a]Isolated as chloride salt; CAS no. of parent compound is 199982-97-3. [b]Oxone manufactured by DuPont (Newark, DE); Fichlor manufactured by Aldrich Chemical Company (Milwaukee, WI).

3.5×10^{-9} atm × m^3/mol (*8*) indicates that VX is essentially nonvolatile from water. VX is moderately persistent on bare ground and may remain in significant concentrations for 2–6 days, depending on temperature, organic carbon content of the soil, and moisture (*246*). In reviewing field and closed container studies of VX persistence, Small (*8*) estimated that 90% of initially applied VX in soil would be lost in ≤ 15 days. In the laboratory, unstabilized VX of 95% purity decomposed at a rate of 5%/month at 22°C (*247*).

The U.S. Army has conducted a sampling and analysis of ton containers of VX stored at the Newport Chemical Activity [(*245*); reviewed by the NRC [*21*] and Amr et al. (*23*)]. According to the NRC (*21*), the VX stored at Newport is 90.5–94.8% pure. It was formulated with 1–3% of the stabilizer diisopropyl carbodiimide to protect it against decomposition from trace amounts of water. During the ensuing 30–40-year storage period, the stabilizer has hydrolyzed, but most of the nerve agent remains intact. Compounds present in ton containers, as identified by gas chromatography, are listed in Table 12.

Rohrbaugh (*249*) identified the following impurities in a stored ton container of VX (identification was by direct gas chromatography-mass spectrometry analysis): diisopropylamine (0.7%), *O,O*-diethyl methylphosphonate (0.6%), *O,O*-diethyl methylphosphonothioate (0.4%), 2-(diisopropylamino) ethane thiol (1.4%), *O,S*-diethyl methylphosphonothioate (0.6%), 2-(diisopropylamino)ethyl vinyl sulfide (0.1%), 2-(diisopropylamino)ethyl ethyl sulfide (0.2%), *O,O*-diethyl dimethylpyrophosphonate (1.6%), *O,O*-diethyl dimethylmonothionopyrophosphonate (0.3%), dicyclohexyl carbodiimide (3.4%), *O*-ethyl *S*-2-(diisopropylamino)ethyl methylphosphonodithioate (0.04%), bis[2-(diisopropylamino)ethyl] sulfide (2.0%), and bis(2-diisopropylaminoethyl) disulfide (0.5%). Bis(*S,S*-(2-(diisopropylamino)ethyl) methylphosphonodithiolate (0.8%) and *O*-ethyl methylphosphonothioic acid (0.2%) were detected by ^{31}P nuclear magnetic resonance. One of these compounds, *O*-ethyl methylphosphonothioic acid, was identified in a soil sample following the destruction of a plant in Khartoum, Sudan, where intelligence sources said VX was being made (*251*). *O*-Ethyl methylphosphonothioic acid is a VX precursor for some processes.

D'Agostino et al. (*250*) previously identified many of the same compounds (present in the ton containers) in a glass container of VX that had been stored for > 10 years. Additional impurities were tentatively identified by combined capillary column gas chromatography–mass spectrometry under both electron impact and chemical ionization conditions. D'Agostino et al. (*252*) then characterized a number of novel polar and higher molecular weight degradation products by liquid chromatography/electrospray mass spectrometry, including phosphorus compounds containing a P–CH_3 bond, long chain bis(diisopropylamino)thiaalkanes, and urea stabilizers.

VX is soluble in water, 30 g/L at 25°C (*8*), and is relatively resistant to hydrolysis (*7*). The reported half-life in water at 25°C and pH 7 ranges from 17 to 42 days (*9*). Hydrolysis proceeds by several pathways, producing a variety of degradation products (*9,13,27,28,248*) (Figure 2 and Table 12). At pH values of < 6 and > 10, cleavage of the P–S bond predominates, resulting in formation of ethyl methylphosphonic acid (EMPA) and diisopropylethyl mercaptoamine (DESH). The latter compound can be oxidized to bis(2-diisopropylaminoethyl) disulfide (EA 4196) or react with the diisopropyl ethyleneimmonium ion $(CH_2)2N + (C_3H_7)_2$ to form bis(2-diisopropylaminoethyl) sulfide. In a solution of 0.01 M VX and aqueous 0.1 M NaOH, VX was hydrolyzed to EMPA and *S*-(2-diisopropylaminoethyl) methylphosphonothioic acid (EA 2192) ions in a ratio of 87% to 13%, respectively; under these conditions, the half-life of VX was 31 min (*253*).

At neutral and alkaline pH values (7–10), the above pathway competes with dealkylation of the ethoxy group (cleavage of the C–O bond), the latter pathway yielding the environmentally stable EA 2192 and ethanol. Although methylphosphonic acid (MPA) can theoretically be formed slowly by hydrolysis of EMPA, it has not been demonstrated to occur in aqueous solutions (*28*). However, Verweij and Boter (*254*) reported the isolation of MPA from VX-contaminated soil. The sulfur-containing products such as EA 2192 are relatively stable in water (*255*); no degradation of EA 2192 was observed after 1,000 hr in distilled water (*256*). The disulfide is also extremely stable in the environment (*257*). Cleavage of the S–C bond may also occur, forming ethyl methylphosphonothioic acid, 2-diisopropylaminoethanol, and diisopropyl ethyleneimmonium ion (*248,258*). According to the NRC (*21*), the impurity, bis, present in ton containers would also hydrolyze to EA 2192.

In another study, Szafraniec et al. (*256*) observed the hydrolysis of 0.5% VX in unbuffered solution at 21°C. Hydrolysis occurred by all three of the above pathways; the reactions were independent of pH. The principal product was EA 2192 (49.4 mol percent). The overall half-life was 57.3 hr.

Laboratory and field studies on the fate of nerve agents in soil indicate that disappearance results from a combination of processes including evaporation, hydrolysis, and microbial degradation. Soil types and properties and the presence/amount of soil moisture and bacteria greatly influence the rate of degradation. Field and closed-container studies indicate that approximately 90% of VX is lost from soil in 15 days (*8*).

In addition to VX, the degradation products diethyl methylphosphonate (an impurity and degradation product) and EA 4196 were identified when soil was spiked with VX in the laboratory and analyzed over a 1-month period. Trace levels of other degradation products were also present (*34*).

Verweij and Boter (*254*) and Kaaijk and Frijlink (*259*) reported rapid degradation of VX with formation of EMPA and DESH. After 1 day, the applied VX concentration of 0.2 mg/g soil decreased to 22% in humic sand and 2% in humic loam and clayey peat. Only 0.1% of applied VX was detectable in all soils after 3 weeks. The half-life of EMPA

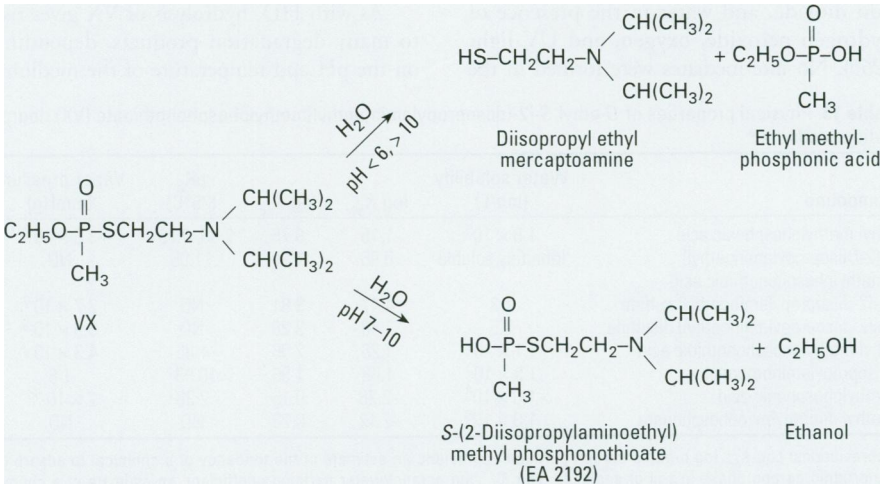


Figure 2. Primary hydrolysis pathways of *O*-ethyl-*S*-[2-(diisopropylamino)ethyl]methylphosphonothioate (VX) in the environment.

was 8 days; the degradation product was MPA. When EMPA was applied to humic sand, approximately 40% hydrolyzed to MPA in 1 day and 80% hydrolyzed in 12 days (*254*). Of the sulfur-containing compounds, only EA 4196 was identified; this compound was tightly bound to the soil (*259*). Binding of the metabolites but not the parent compound correlated positively with the amount of organic matter in the soil. Small (*8*) pointed out that VX degradation products sorb to soil depending on the soluble organic carbon content of the soil. Diethyl dimethylpyrophosphonate may also be formed from EMPA in soil (*8*).

In field studies conducted at Carroll Island, Maryland (*8*), VX sprayed on soil decreased by about three orders of magnitude within 17–52 days. In an area of field tests at Dugway Proving Ground, where soil levels before 1969 were as high as 6 mg/g, no VX was detected (detection limit 0.4 µg/g) 10 years later. The degradation product, MPA, was detected at concentrations ranging from 14.9 to 23 µg/g and was distributed uniformly through a 120-cm depth.

Small (*8*) compiled physical properties that pertain to the environmental fate of several of the major degradation products (Table 13). EA 2192, a white solid at ambient temperature, is both infinitely soluble and extremely stable in water at neutral and alkaline pHs (*255,256*). It is more stable to hydrolysis than VX: in a solution of 0.1 N NaOH and temperature of 25°C, no significant hydrolysis occurred within 12 days. A log K_{oc} of 1.90 (*8*) indicates a low potential to adsorb to soil. A low log K_{ow} (*8*) indicates little potential to bioaccumulate. Its vapor pressure is extremely low (*13*).

EMPA is resistant to hydrolysis but, as noted above, disappears fairly rapidly from soil. Kingery and Allen (*28*) listed degradation rate constants in water and soil of 2.4×10^{-10} and 3.6×10^{-3} (per hour at 25°C), respectively. The data in Table 13 indicate a high water solubility and a low volatility.

MPA is stable in the environment because it is resistant to hydrolysis, photolysis, and thermal decomposition (*34,263*). The rate of disappearance of MPA in environmental media is controlled by biodegradation (*28*); however, the C–P bond is resistant to cleavage (*263*). Based on a Henry's Law constant of 1.22×10^{-11} atm × m^3/mol at 25°C, MPA is not expected to volatilize from water or moist soils. An estimated vapor pressure of > 2×10^{-6} mmHg indicates that MPA may exist in very small amounts in the particulate and vapor phases in the atmosphere (*263*). MPA has been predicted to be infinitely soluble in water and highly mobile in soils [log K_{oc} of 0.15; (*8*)]. At environmentally relevant pH values (pH 5–9), MPA, EMPA, and ethyl methylphosphonothioic acid will be highly dissociated in water (*263*) (pK_a values are presented in Table 13). Based on a low log K_{ow} of -2.28, MPA is not expected to bioconcentrate in aquatic organisms. MPA may be released to the environment during its use as a chemical warfare simulant and during manufacture of a variety of structurally similar compounds (*263*). It may also be released to the environment from degradation of pesticides such as *O,O*-bis(2,4,5-trichlorophenyl) methylphosphonate and flame retardants such as dimethyl methylphosphonate, Fyrol 58 (Akzo Nobel, Gallipolis Ferry, OH), and Antiblaze 19 (Albright & Wilson, Richmond, VA) (*263*).

Decontamination. VX undergoes water and hydroxyl ion-catalyzed hydrolysis but is not subject to acid-catalyzed hydrolysis (*13*). Thus, the proposed neutralization technology for agent VX, although similar to that for agent HD, uses alkaline rather than neutral-to-acidic conditions (*21*). Neutralization with aqueous NaOH at 90°C for 6 hr and oxidation of the hydrolysate with dilute sodium hypochlorite solution (*21*) should be followed by either on-site or off-site supercritical water oxidation (*22*). The hydrolysate from NaOH treatment has been characterized and includes the following degradation products: EMPA, MPA, diisopropylaminoethane thiol, bis(diisopropylaminoethyl) disulfide, bis-(diisopropylaminosulfide), 1,9-bis(diisopropylamino)-3,4,7-trithianonane, other diisopropylaminoethane compounds, *N,N'*-methanetetrayl bis(cyclohexanamine), and mono(2-ethylhexyl)ester hexanedioic acid (*264*). EMPA and diisopropylaminoethane thiol were the major components.

Bleach and Fichlor (*N,N*-dichloroisocyanurate; Aldrich Chemical Company, Milwaukee, WI) effectively oxidize/detoxify VX, forming EMPA and a sulfonic acid (*29*). MPA can be oxidized to phosphoric acid, carbon dioxide, and water in the presence of hydrogen peroxide, oxygen, and UV light (*265*). No intermediates were formed in the case of MPA. In aqueous or aqueous polar organic solvents, VX is rapidly oxidized by strong peroxyacids such as the peroxymonopersulfate in oxone, magnesium monoperoxyphthalate, peroxyacetic acid, and *m*-chloroperoxybenzoic acid (*266*). Nucleophilic substitution with P–S bond cleavage takes place with aqueous peroxycarbonate. These and additional neutralization reactions for VX were summarized by Yang (*266,267*).

In reviewing the studies of Yang et al. (*258*) and others, Rosenblatt et al. (*13*) suggested that under strongly basic conditions with an alcoholic solvent, P–S cleavage is favored and VX could be decontaminated without the formation of EA 2192. Perhydrolysis of VX (substitution with HO_2^-) is extremely rapid and also proceeds without the formation of EA 2192 (*253*). The stabilizer diisopropylcarbodiimide and/or its hydrolysis product 1,3-diisopropylurea are oxidized by supertropical bleach to *N*-chloroisopropylamine (*8*).

Acute and chronic mammalian toxicity. The organophosphate nerve agent VX is a potent anticholinesterase agent that can act by dermal, oral, or inhalation routes of exposure. Some signs and symptoms of exposure include miosis, nausea, tightness in the chest, increased salivation and sweating, and lacrimation. In sufficient concentrations VX causes death by compromising respiration (it causes copious secretions, paralyzes the respiratory muscles, and inhibits the respiratory center of the brain) (*1*). The anticholinesterase mechanism of action of organophosphonic acids such as VX is due to the oxo (=O) group, but is also influenced by the presence of alkyl substituents. Thus, initial degradation products may retain some anticholinesterase activity, but hydrolysis of one or more alkyl ester bonds of organophosphonic acids results in the generally nontoxic alkyl methylphosphonic acids.

As with HD, hydrolysis of VX gives rise to many degradation products, depending on the pH and temperature of the medium.

Table 13. Physical properties of *O*-ethyl *S*-[2-(diisopropylamino)ethyl]methylphosphonothioate (VX) degradation products.[a]

Compound	Water solubility (mg/L)	log K_{ow}	log K_{oc}	pK_a (25°C)	Vapor pressure (mmHg)
Ethyl methylphosphonic acid	1.8×10^5	-1.15	0.75	2.00, 2.76[b]	3.6×10^{-4}
S-(2-Diisopropylaminoethyl) methylphosphonothioic acid	Infinitely soluble	0.96	1.90	11.05	ND
Bis(2-diisopropylaminoethyl) sulfide	1.2	4.47	3.81	ND	2.7×10^{-7}
Bis(2-diisopropylaminoethyl) disulfide	9.5	3.48	3.28	ND	5.9×10^{-9}
Ethyl methylphosphonothioic acid	1.1×10^3	1.26	2.06	1.85	4.3×10^{-2}
Diisopropylaminoethanol	1.5×10^3	1.08	1.96	10.08[c]	1.8
Methylphosphonic acid	$> 1.0 \times 10^6$	-2.28	0.15	2.38	2×10^{-6}[d]
Diethyl dimethylpyrophosphonate	$> 1.0 \times 10^6$	-2.12	0.23	ND	ND

Abbreviations: Log K_{oc}, log organic carbon partition coefficient, an estimate of the tendency of a chemical to adsorb to the organic carbon phase in soil or sediment; Log K_{ow}, log octanol/water partition coefficient, an estimate of a chemical's tendency to bioaccumulate in organisms; ND, no data.
[a]Modified from Small (*8*) except where otherwise indicated. [b]Data from Bossle et al. (*260*). [c]Estimated from the Hazardous Substances Data Base (*261*). [d]Data from Howard and Meylan (*262*).

Little is known about the toxicity of most of these hydrolysis products, although one or more retain anticholinesterase activity (e.g., EA 2192). The VX degradation products for which acute toxicity data could be located are listed in Table 14. No information was located on the chronic toxicity of any VX hydrolysis product. Other long-term effects and mutagenicity and reproductive effects are summarized in Table 15.

In the absence of an adequate database to calculate safe levels for chronic exposures to VX degradation products and impurities, the U.S. Army Center for Health Promotion and Preventive Medicine has estimated RfD and RfC values using data from structurally related compounds and/or QSAR using TOPKAT software (*298*). RfCs were calculated

Table 14. Effects of acute exposure to *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX) degradation products, stabilizers, and impurities.

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
VX hydrolysis			
Diisopropyl ethyl mercaptoamine (DESH) ($C_8H_{19}NS$; 5842-07-9)	Mouse: ip, 5 mg/kg (*268*)		
S-(Diisopropylaminoethyl) methyl phosphonothionate (EA 2192) ($C_9H_{22}NPO_2S$; 73207-98-4)	Rat: oral, 630 µg/kg (*256*) Rat: iv, 18 µg/kg (*256*) Mouse: iv, 50 µg/kg (*269*) Rabbit: iv, 0.017 mg/kg (*258*) Rabbit: iv, 12 µg/kg (*269*)		
2-Diisopropylaminoethanol ($C_8H_{19}NO$; 96-80-0)	Rat: oral, 860 mg/kg (*270*) Rat: oral, 1,070 mg/kg (*70*) Mouse: oral, 770 mg/kg (*270*) Rabbit: skin, 450 µL/kg (*70*) Rat: inhalation, 1,965 mg/m^3/6 hr (*270*) Mouse: inhalation, 1,661 mg/m^3/6 hr (*270*)		Rabbit: skin irritant, severe corrosive (*270*) Rabbit: skin irritant, mild (*70*) Rabbit: skin irritant, 500 mg open, mild (*271*) Rabbit: eye irritant, 750 µg open, severe (*70*)
Diethyl methylphosphonate ($C_5H_{13}O_3P$; 683-08-9)	Mouse: ip, 2,240 mg/kg (*272*)		
Methylphosphonic acid (MPA) (CH_5O_3P; 993-13-5)	Rat: oral, 5,000 mg/kg (*273*) Mouse: oral, > 5,000 mg/kg (*273*)		Human: skin and eye irritant (*274*)
Diethyl dimethyl pyrophosphonate ($C_6H_{16}P_2O_5$; 32288-17-8)	Rabbit: skin, 7.1 mg/kg (*258*)		
O,S-diethyl methylphosphonothioate ($C_5H_{13}O_2PS$; 2511-10-6)	Rat: oral, 6.0 mg/kg (*275*) Dog: iv, 5,620 µg/kg (*276*) Mouse: iv, 1 mg/kg (*276*) Rabbit: iv, 2,480 µg/kg (*276*)		
VX decontamination, impurity in ton containers			
Diisopropylamine[a] ($C_6H_{15}N$; 108-18-9)	Rat: oral, 770 mg/kg (*70*) Mouse: oral, 2,120 mg/kg (*279*) Rabbit: oral, 4,700 mg/kg (*279*) Guinea pig: oral, 2,800 mg/kg (*279*) Rabbit: skin, > 10 g/kg (*282*)	Rat: inhalation, 4,800 mg/m^3/2 hr (*127*) Rat: inhalation, < 2,200 ppm/3 hr; > 777 ppm/7 hr (*280*) Mouse: inhalation, 4,200 mg/m^3/2 hr (*127*) Cat: inhalation, 2,207 ppm/72 min (*277*) Rabbit: inhalation, 2,207 ppm/2.5 hr (*277*) Guinea pig: inhalation, 2,207 ppm/82 min (*277*)	Human: vision disturbances, nausea and headache, 25–50 ppm (*277,278*) Several species: cloudy swelling of corneal epithelium, > 600 ppm (*277*) Rabbit: mild skin irritant, 500 mg/24 hr (*110*) Guinea pig: severe skin irritant, 3 weeks (*281*) Rabbit: severe eye irritant, 750 µg open (*70*)
VX stabilizers and decontaminant products			
Diisopropylcarbodiimide ($C_7H_{14}N_2$; 693-13-0)	Mouse: iv, 36 mg/kg (*283*)		Human: severe eye irritation, temporary blindness (*284*)
Dicyclohexylcarbodiimide ($C_{13}H_{22}N_2$; 538-75-0)	Rat: oral, ~ 400 mg/kg (*285*) Mouse: oral, > 800 mg/kg (*285*) Guinea pig: dermal, 1–5 drops (*285*) Rat: inhalation, 0.159–0.417 mg/L (*285*)		Guinea pig: skin, moderate irritant (*285*) Rabbit: eye, severe irritant (*285*) Rat: inhalation, lung inflammation, focal atrophy of stomach, liver necrosis, testicular atrophy (*285*)
Chloroform[b] ($CHCl_3$; 67-66-3)	Rat: oral, 908 mg/kg (*83*) Mouse: oral, 36 mg/kg (*88*) Dog: oral, 1 g/kg (*90*) Guinea pig: oral, 830 mg/kg (*92*) Rat: inhalation, 47.7 mg/m^3/4 hr (*94*) Rabbit: dermal, > 20 g/kg (*96*)	Human: oral, 2,514 mg/kg (*84*) Human: inhalation, 10 ppm/year (*89*) Human: inhalation, 1,000 mg/m^3/7 min (*76*) Human: inhalation, 5,000 mg/m^3/7 min (*93*) Dog: inhalation, 100 g/m^3 (*95*) Cat: inhalation, 35,000 mg/m^3/4 hr (*93*) Guinea pig: inhalation, 20,000 ppm/2 hr (*97*) Rabbit: inhalation, 59 g/m^3 (*95*) Rat: inhalation, 8,000 ppm/4 hr (*76*) Mouse: inhalation, 28 g/m^3 (*85*) Human: 546 mg/kg (*98*)	Human: eye, pain, irritation, and anesthesia, central nervous system depression, death from cardiac or respiratory arrest; liver and kidney damage (*85–87*) Rabbit: skin, irritant, 10 mg/24 hr (*76*) Rabbit: eye irritant, 148 mg (*91*)

Abbreviations: ip, intraperitoneal; iv, intravenous; LC_{50}, median lethal concentration; LC_{LO}, lowest lethal concentration; LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose.
[a]Diisopropylamine is a potential product of VX decontamination with supertropical bleach, resulting from reaction with the hypochlorite constituent. [b]Chloroform is another possible product of VX decontamination with supertropical bleach.

from the corresponding RfDs. These provisional RfDs and RfCs for 25 degradation products, impurities, and stabilizers are listed in Table 16. These values are provisional and, therefore, subject to change.

EA 2192, one of the initial VX hydrolysis products formed between pH 7 and 10, has anticholinesterase activity similar to VX. Its intravenous toxicity is somewhat lower (0.24–0.825 that of VX, depending on the species) but approximately equivalent to VX (Table 14) (*255*). However, its oral lethality of 630 µg/kg in the rat (*255*) is only 0.1–0.2 that of liquid VX in the same species [VX oral LD_{50} of 100 µg/kg (*228*) or 66 µg/kg, (*299*)]. Furthermore, EA 2192 was without effect when dissolved in water or alcohol and applied to the clipped backs of rabbits (for up to 24 hr in water solution). Only when dissolved in di-*n*-hexylamine did it penetrate the skin and produce lethality (*255*). Another source gives a rabbit dermal LD_{50} of 1.4 mg/kg without specifying the vehicle (*15*). This is ≤ 0.02 times that of VX in the rabbit (*228*). Rosenblatt et al. (*13*) considered EA 2192 insufficiently volatile to be an inhalation hazard. Thus, in environmentally relevant situations, EA 2192 is not absorbed through the skin and not likely to be inhaled; only the oral route of exposure remains a concern. It is not clear whether EA 2192 is sufficiently persistent in the environment to be of concern. Under laboratory conditions this compound can attain concentrations of approximately 40% in a hydrolysate mixture at pH 7.2 (*6,27*). However, it is expected to be totally destroyed by the proposed hot alkaline hydrolysis disposal process for VX (*21*). In view of the iv toxicity of EA 2192, Bausum (*298*) proposed that an RfD for EA 2192 be based on the interim RfD for VX of 0.0006 µg/kg/day [Table 16 (*19*)], which was derived from a sheep lowest-observed-adverse-effect level (LOAEL) of 0.06 µg/kg/day for whole blood cholinesterase inhibition. This RfD should be protective in view of the lesser EA 2192 toxicity by either oral or dermal routes.

Although information is limited about other VX hydrolysis products, none display the high acute toxicity of EA 2192, and most for which information is available can be characterized as having low-to-moderate acute lethality. Diisopropyl ethyl mercaptoamine, for example, has an ip LD_{50} value of 5 mg/kg in the mouse in the one available study (*268*) (Table 14); the LD_{50} for VX is 0.038 mg/kg by the same route (*228*). No toxicity data were found for EMPA, but it is structurally similar to isopropyl methylphosphonic acid (IMPA) and it may be expected to have the same low-to-moderate toxicity as IMPA and MPA (Table 14). A QSAR-based rat oral LD_{50} value of 65 mg/kg has been estimated for EMPA (*298*). Bausum et al. (*190*) estimated an RfD for EMPA of 25 µg/kg/day based on the rat subchronic NOAEL of 279 mg/kg/day for the related compound IMPA and the addition of several uncertainty factors (Table 16). Limited data for MPA suggest low oral toxicity in the rat and mouse, with LD_{50} values of ≥ 5,000 mg/kg [Table 14; (*273*)]. MPA is considered a human skin and eye irritant (*274*), although no regulatory levels have been established. Using TOPKAT, a preliminary QSAR-based estimate for the rat chronic LOAEL was 566 mg/kg/day [lower confidence limit = 123 mg/kg/day; (*190,298*)]. Bausum (*298*) based a provisional RfD estimate for MPA of 57 µg/kg/day on the QSAR-derived LOAEL. However, a preferred RfD value for MPA of 20 µg/kg/day was derived from the subchronic rat NOAEL of 279 mg/kg/day for the closely related compound IMPA (*190*).

The hydrolysis product 2-diisopropylaminoethanol causes mild skin irritation and severe eye irritation in rabbits and is moderately toxic in acute animal studies by several routes of exposure (Table 14). Another hydrolysis product, diethyl methylphosphonate, appears to have moderately low acute toxicity in mice exposed by ip injection (LD_{50} = 2,240 mg/kg), although only one value was located (Table 14).

VX impurities such as *O,S*-dialkyl alkylphosphonothioate esters have an anticholinesterase mechanism of action and high acute toxicity. The oral LD_{50} of *O,S*-diethyl methylphosphonothioate for the rat is 6.0

Table 15. Carcinogenicity, genotoxicity, reproductive toxicity[a], and systemic effects of chronic exposure to *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX) degradation products and stabilizers.

Degradation product (formula; CAS no.)	Carcinogenicity	Genetic effects	Systemic effects
VX decontamination			
Diisopropylamine[b] ($C_6H_{15}N$; 108-18-9)		Mutagenicity: negative, Ames (*224*) Mutagenicity: questionably positive, Ames, 1 µg/plate (*278, 286*) DNA repair: negative, rat hepatocyte primary culture assay (*281*)	Guinea pig: sensitizer, negative (*281*)
Chloroform[c] ($CHCl_3$; 67-66-3)	Probable human carcinogen (*142,143*) Rat: positive (*87*) Mouse: positive (*87*) Rat: positive, mouse: negative (*150*)	Mutagenicity: Ames, negative (*144*) Mutagenicity: yeast, positive (*146*) Mutagenicity: mouse, positive (*145*) Chromosome effects: human lymphocytes, negative (*151*) SCE: *in vitro*, low or negative (*152–154*) SCE: mouse, *in vivo*, positive (*154*) Micronucleus: negative (*155*) Delayed cell cycle: human lymphocytes, positive (*154*)	Human: hepatomegaly, fatty liver degeneration, toxic hepatitis (*87*) Human: central nervous system, psychiatric, neurologic effects (*148*)
VX stabilizers			
Diisopropylcarbodiimide ($C_7H_{14}N_2$; 693-13-0)	Carcinogenicity: negative, 20-week prechronic studies, female mice (*287,288*)	Mutagenicity: negative, Ames (*289*) Cytogenicity: negative, micronucleus induction, Fischer 344 rat (*291*) Cytogenicity: positive, micronucleus induction, $B6C3F_1$ mouse (*291*)	Human: contact allergen (*290*) Mouse: skin sensitizer (*292*)
Dicyclohexylcarbodiimide ($C_{13}H_{22}N_2$; 538-75-0)	Mouse: likely animal carcinogen (*293,294*)	Mutagenicity: negative, Ames (*295*) Cytogenicity: positive, micronucleus, $B6C3F_1$ mice (*296*) Cytogenicity: negative, micronucleus, Fischer 344 rat (*296*)	Human: contact allergen (*290*) Mouse: skin sensitizer (*297*)

[a]Reproductive effects were observed only with chloroform; fetotoxic, retarded development, and teratogenic in the rat (*145*); sperm abnormalities in the mouse (*147*); and negative in sperm morphology assay in the mouse (*149*). [b]Diisopropylamine is a potential product of VX decontamination with supertropical bleach, resulting from reaction with the hypochlorite constituent. [c]Chloroform is another possible product of VX decontamination with supertropical bleach.

mg/kg (Table 14). Like most impurities, this compound is present at < 1% in ton containers.

The VX stabilizer diisopropylcarbodiimide produces severe eye irritation and temporary blindness in humans (*284*). There is one systemic toxicity data point for the mouse, an LD_{50} value of 36 mg/kg by the iv route [Table 14; (*283*)]. This indicates acute iv toxicity about 0.0004 that of VX (*228*). Diisopropylcarbodiimide is a contact allergen in humans [Table 1; (*290*)] and a skin sensitizer in mice (*292*). It was negative for carcinogenicity in 20-week prechronic studies in mice (*287,288*), although testing is not complete (Table 14). It gave negative results in the Ames test for mutagenicity and for micronucleus induction in rats, but was positive for micronucleus induction in mice (*289,291*) (Table 15).

Diisopropylamine, found in minute amounts in ton containers of VX and also a potential product of reaction with hypochlorite, is a severe primary pulmonary irritant. Superficial contact causes corneal degeneration and cloudy swelling in several animal species upon exposure to concentrations ≥ 600 ppm (*167*). Diisopropylamine causes vision disturbances, nausea, and headache in humans at 25–50 ppm (*277,278*). It also causes lethality by acute oral, dermal, and inhalation exposure in several species and is more toxic than isopropylamine or the closely related diethyl- and ethylamines (*167*) (Table 14). Diisopropylamine produced negative or equivocal results in the Ames test for mutagenicity (Table 15) and was negative in inducing DNA repair (*281*). It also was negative as a sensitizer in guinea pigs (*281*). The TLV-TWA for this chemical is 5 ppm (~ 21 mg/m^3) (*196*). The OSHA PEL is the same (*197*). A provisional RfD of 0.43 µg/kg/day has been calculated (*298*).

Chloroform is also a possible product of VX reaction with STB (*8*). Its evaluation is presented in the "Sulfur Mustard" section (Tables 4 and 5).

Ecotoxicology. All of the nerve agents are highly toxic to aquatic organisms, with 96-hr LC_{50} values (the normal duration of fish toxicity tests) of < 1 mg/L. Weimer et al. (*300*) measured the LT_{50} (time to lethality for 50% of the organisms) of VX for striped bass (*Morone saxatilis*) at 0.02 mg/L as 17.4 hr. Except for MPA, ecotoxicity data were not located for VX degradation products.

The following aquatic toxicity data were located for MPA: 48-hr LC_{50} for *Daphnia magna* = 3,273 mg/L; 96-hr LC_{50} values for fathead minnows and bluegill sunfish = 10,617 and 12,380 mg/L, respectively; 14-day EC_{50} for cell numbers of *Selenastrum capricornutum* = 17,805 mg/L; and 7-day EC_{05} (concentration effective for 5% of the taxa) for colonizing ability of freshwater protozoan communities (taxonomic richness) = 581 mg/L (*273*).

GA

The chemical and physical properties of GA, or tabun, are listed in Table 1. GA is a colorless to brownish liquid that gives off a colorless vapor. Its vapor pressure and volatility, 0.037 mmHg and 610 mg/m^3 at 20°C, respectively, are the lowest of the G agents. Although water soluble (98 g/L), it is also readily soluble in organic solvents and thus easily penetrates the skin. GA enters the body mainly through the respiratory tract and its primary action is on the respiratory tract, although it also causes impaired vision via its anticholinesterase action (*11*).

GA was the first nerve agent to be put into production; it was discovered by the Germans in 1937, and large-scale production and stockpiling began in 1942 (*99*). In the United States, GA was produced in very small quantities as compared to GB, VX, or HD. Nonstockpile material in glass ampules (0.07 lb total material) is stored in a drum at Tooele

Table 16. Estimated reference doses (RfDs) and reference concentrations (RfCs) for *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate (VX) degradation and related products.[a]

Degradation product (formula; CAS no.)	RfD (µg/kg/day)	RfC (µg/m^3)
Ethyl methylphosphonic acid ($C_3H_9PO_3$; 1832-53-7)	25	30
Diisopropyl ethyl mercaptoamine ($C_8H_{19}NS$; 5842-07-9)	3.8	4.6
S-(Diisopropylaminoethyl) methylphosphonothioic acid ($C_9H_{22}NPO_2S$; 73207-98-4)	0.0006	0.0007
Bis(2-diisopropylaminoethyl) sulfide ($C_{16}H_{36}N_2S$; 110501-56-9)	8.6	10.3
Bis(2-diisopropylaminoethyl) disulfide ($C_{16}H_{36}N_2S_2$; 65332-44-7)	6.6	7.9
O-Ethyl methylphosphonothioic acid ($C_3H_9O_2PS$; 18005-40-8)	7	8.5
2-Disopropylaminoethanol ($C_8H_{19}NO$; 96-80-0)	8.4	10
Methylphosphonic acid (CH_5O_3P; 993-13-5)	20	24
Bis(*S,S*-(2-diisopropylaminoethyl) methylphosphonodithiolate ($C_{17}H_{39}N_2PS_2$; 169493-13-4)	0.0006	0.0007
2-(Diisopropylamino) ethyl ethyl sulfide ($C_{10}H_{23}NS$; not available)	8.6	10.3
Diethyl methylphosphonate ($C_5H_{13}O_3P$; 683-08-9)	29	35
1,2-Bis(ethyl methylphosphonothiolo) ethane (not available; not available)	5.0×10^{-5}	6.0×10^{-5}
O-(2-Diisopropylaminoethyl) *O'*-ethyl methylphosphonate ($C_{11}H_{26}NO_2P$; 71840-26-1)	0.025	0.03
O,O-Diethyl *P,P'*-dimethyldiphosphonothionate (not available; not available)	0.05	0.06
O,O-Diethyl methylphosphonothioate ($C_5H_{13}O_2PS$; 6996-81-2)	12	13
O-Ethyl methylethylphosphinate (not available; not available)	14	17
Diethyl dimethylpyrophosphonate ($C_6H_{16}O_5P$; 32288-17-8)	0.05	0.06
O,S-Diethyl methylphosphonothioate ($C_5H_{13}O_2PS$; 2511-10-6)	0.017	0.02
Diisopropylamine ($C_6H_{15}N$; 108-18-9)	4.3	5.1
N,N-Diisopropylmethylamine ($C_7H_{17}N$; 10342-97-9)	0.56	2
N,N-Diisopropylethylamine ($C_8H_{19}N$; 7087-68-5)	0.56	2
Diisopropyl carbodiimide ($C_7H_{14}N_2$; 693-13-0)	0.25	0.3
Dicyclohexyl carbodiimide ($C_{13}H_{22}N_2$; 538-75-0)	0.25	0.3
1,3-Diisopropylurea ($C_7H_{16}N_2O$; 4128-37-4)	0.87	1.04
1,3-Dicyclohexylurea ($C_{13}H_{24}N_2O$; 2387-23-7)	6.7	8

[a]RfD estimates are based on data from structurally related chemicals or from quantitative structure–activity relationship estimates using TOPKAT software (Health Designs, Inc., Rochester, NY). Data from Bausum et al. (*190*) and Bausum (*298*).

Army Depot. Stockpiled amounts include 1.41 tons of the agent stored in two 1-ton containers and 0.64 tons of the thickened agent stored in two 1-ton containers (*25*). Nonstockpiled GA may also be present at several other sites including Edgewood Arsenal, Maryland; Dugway Proving Ground; and the Virgin Islands (*230,231*). It seems reasonable to presume that the sites are potentially contaminated with GA, and its degradation products are somewhat limited in comparison to the major chemical warfare agents.

GA is seldom found in pure form; it is generally contaminated with degradation products or production by-products. D'Agostino and colleagues (*301*) analyzed a munitions-grade sample of GA and found that impurities accounted for 28% of the volatile organic content. The principal impurity of a munitions-grade sample was diethyl dimethylphosphoramidate (*302*). Analysis of a 30-year-old sample found only 76% GA, with the impurities *O,O*-diethyl *N,N*-dimethylphosphoramidate, *O*-ethyl bis(*N,N*- dimethyl)phosphorodiamidate, and *O*-ethyl *O*-isopropyl *N*-dimethylphosphoramidate accounting for 12, 5, and 5% of the sample, respectively (*303*). Except for triethyl phosphate and tetramethylphosphorodiamidic cyanide, which are both present at approximately 1%, all other impurities are present at < 1%. GA usually contains a thickener.

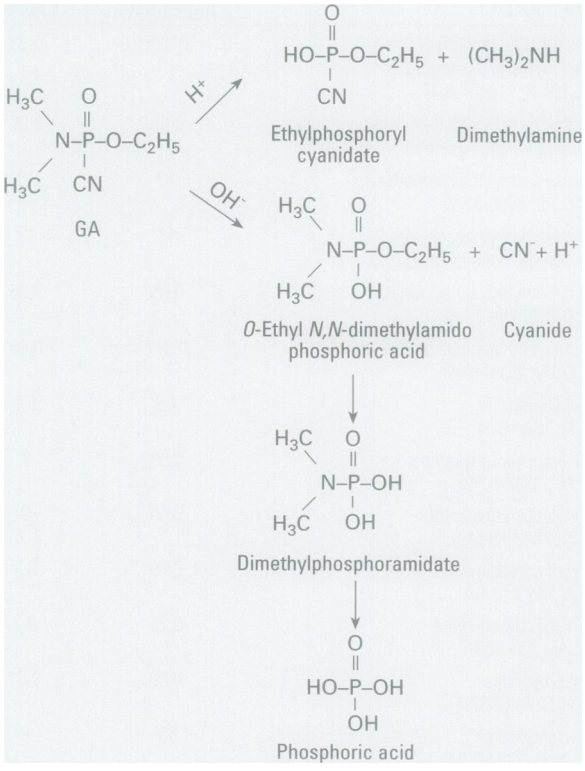


Figure 3. Primary hydrolysis pathways of ethyl *N,N*-dimethylphosphoroamidocyanidate (tabun; GA) in the environment.

Formation of degradation products. GA is more volatile than VX and will evaporate, but no data were located on concentrations or fate in the atmosphere.

GA is subject to hydrolysis (Figure 3). The principal pathway under neutral conditions in the environment is hydrolysis to *O*-ethyl *N,N*-dimethylamido phosphoric acid and hydrogen cyanide. The initial reaction is fairly rapid; hydrolysis of *O*-ethyl *N,N*-dimethylamido phosphoric acid to dimethyl phosphoramidate and then to phosphoric acid is much slower. Although this latter pathway predominates under neutral and basic conditions, phosphorocyanidate may also be formed from dimethyl phosphoramidate. Under acidic conditions, hydrolysis to ethylphosphoryl cyanidate and dimethylamine occurs. The final product by all pathways is phosphoric acid. Although theoretically possible, there is little likelihood of formation of a detectable amount of MPA from GA (*34*).

Hydrolysis is more rapid in acidic and basic solutions than in solutions of neutral pH. The rate also increases with increasing temperature. At neutral pH and 25°C, GA persists in water for 14–28 hr (*44*); the half-life at 20°C and pH 7.4 is approximately 8 hr (*9*). However, MacNaughton and Brewer (*27*) list a longer half-life at pH 3 (14 hr) than at pH 5 (2.5 hr). Because of the formation of acidic products, a solution of GA approaches pH 4–5 as it hydrolyzes. The half-life in seawater at 20°C is shorter (4.5 hr) than in freshwater (*9*). Hydrolysis products and contaminants are listed in Table 17.

In soil, nerve agents may be transformed by microbial degradation via *O*-dealkylation and *C*-dealkylation; nitrile hydrolysis and *N*-dealkylation may also occur (*44*). Although Morrill et al. (*44*) stated that some of the products were toxic, they did not identify the toxic products. D'Agostino and Provost (*302*) analyzed soil contaminated by a leaking container of GA collected during range clearance operations. In addition to GA they isolated 16 related components including impurities and hydrolysis products, many of them present in trace amounts (< 1%). These were diethyl dimethylphosphoramidate, triethyl phosphate, ethyl tetramethyl phosphorodiamidate, tetramethylphosphorodiamidic cyanide, bis(ethyl dimethylphosphoramidic) anhydride, dimethyl phosphoric ethyl dimethylphosphoramidic anhydride, ethyl dimethylphosphoramidic tetramethylphosphorodiamidic anhydride, bis(ethyl dimethylamidophosphonyl) dimethylamidophosphonate, ethyl hydrogen dimethylphosphoramidate, diethyl hydrogen phosphate, ethyl dihydrogen phosphate, phthalate, and four unidentified components. D'Agostino et al. (*301*) identified the first seven compounds as impurities in munitions-grade GA. In addition, the following compounds were tentatively identified in the sample: diisopropyl dimethylphosphoramidate, ethyl isopropyl dimethylphosphoramidate, triisopropyl phosphate, diisopropyl ethyl phosphate, diethyl isopropyl phosphate, isopropyl tetramethylphosphoramidate, isopropyl dimethylphosphoramidocyanidate, diethyl phosphoric diisopropyl phosphoric anhydride, diisopropyl phosphoric ethyl dimethylphosphoramidic anhydride, diethyl phosphoric ethyl isopropyl phosphoric anhydride, diethyl phosphoric isopropyl dimethylphosphoramidic anhydride, and bis(diethyl phosphoric) anhydride. These tentatively identified compounds are not included in Table 17.

No data were located on the fate of unique degradation products. Sanches et al. (*34*) reported that many of the GA phosphorus-containing products/contaminants are likely to be degraded to phosphoric acid; other products formed may be similar to products formed from common organophosphorus chemicals. Dimethylamine and triethyl phosphate are readily biodegraded (*205*). Most of the unique impurities are present in trace amounts in munitions-grade GA and thus should be of minimal environmental concern.

Persistence depends on moisture and weather conditions. According to a U.S. Army manual (*11*), liquid GA may persist for 1–2 days under average weather conditions. GA evaporates about 20 times more slowly than water. The calculated Henry's Law constant of GA, 1.52×10^{-7} atm × m^3/mol, indicates slow to essentially no volatilization from water. Studies of the persistence of nerve agents performed at low temperatures (-1°C) under actual field conditions in Norway show that agents placed on snow as droplets remained as liquids on snow (*42,43*). GA was present 2 weeks after being sprayed on snow under normal Norwegian winter conditions but was not measurable after 4 weeks. GA and other nerve agents did not penetrate deeply into the snow, and later snowfalls that covered the samples delayed evaporation.

Decontamination. No specific information was located on the decontamination of

GA. Other G agents are rapidly hydrolyzed by water, particularly under alkaline conditions. Sodium hypochlorite is expected to be an effective decontaminant (*6*). G agents do not react with chlorine dioxide and several other decontaminants but would react with DS-2 (*13*).

After decontamination of GA with methanol-potassium hydroxide and extraction into dichloromethane, the major product identified was the methanolysis product ethyl methyl dimethylphosphoramidate (*305*). Methyl tetramethylphosphorodiamidate and dimethyl dimethylphosphoramidate probably resulted from methanolysis of tetramethylphosphorodiamidic cyanide. Several other GA contaminants were present in the extracts, but pyrophosphates were not observed in the dichloromethane extracts.

Acute and chronic toxicity. The G agents are, like VX, anticholinesterase organophosphate nerve agents that at sufficient concentrations can be toxic or fatal by any route of exposure. Differences in volatility and water solubility result in varied degrees of persistence and variations in the likelihood of exposure by certain routes. For example, the most volatile G agent, GB, is not likely to present a dermal exposure hazard, at least when present at the low residual concentrations expected in the environment. Of the G agents, GA (tabun) gives rise to the greatest number of degradation products (Table 17).

Acute toxicity data are available only for a limited subset of the GA degradation products (Table 18), and chronic and other toxicity data are available for even fewer products (Table 19). Hydrolysis gives rise to dimethylamine, among other substances. Dimethylamine is readily absorbed orally and by inhalation in experimental animals. This chemical is moderately toxic in terms of acute lethality (Table 18) but causes human nose, throat, and lung irritation at 100 ppm and severe burns to the human eye and skin upon direct contact with the liquid (*307*). In comparison to ammonia, dimethylamine is somewhat more locally irritating, as it is a somewhat stronger base (*157*). Oral exposure in animals results in marked gastric mucosal irritation and, at lethal doses, hemorrhages (*306*). Dimethylamine does not appear to be mutagenic, clastogenic, or carcinogenic to rats or mice given long-term inhalation exposure (*157,307*). The OSHA PEL-TWA of 10 ppm (*197*) is higher than the TLV-TWA of 5 ppm (9.2 mg/m^3) (*196*). The ACGIH

Table 17. Degradation products and impurities of ethyl *N,N*-dimethylphosphoroamidocyanidate (tabun; GA).

Name/synonyms	Formula	CAS no.	Source
O-Ethyl-*N,N*-dimethylamido phosphoric acid Ethyl-*N,N*-dimethyl phosphoramidate (EDPA) Ethyl hydrogen dimethylphosphoramidate	$C_4H_{12}NPO_3$	2632-86-2	Hydrolysis of GA
Dimethylphosphoramidate *N,N*-Dimethylphosphoramidate Dimethyl phosphoramidic acid	$C_2H_8NPO_3$	33876-51-6	Hydrolysis of GA
Dimethylphosphoramide cyanidate Phosphoramidocyanidic acid	$C_3H_7N_2PO_2$	63917-41-9	Hydrolysis of GA
Phosphorocyanidate Phosphorisocyanatidous acid	CH_2NPO_3	23852-43-9	Hydrolysis of GA
Ethylphosphoryl cyanidate	$C_3H_6NPO_3$	117529-17-6	Hydrolysis of GA
Dimethylamine	C_2H_7N	124-40-3	Hydrolysis of GA
Ethyl phosphoric acid	$C_2H_7PO_4$	NA	Hydrolysis of GA
Phosphoric acid	H_3PO_4	7664-38-2	Hydrolysis of GA
O,O-Diethyl *N,N*-dimethylphosphoramidate Diethyl dimethylphosphoramidate	$C_6H_{16}NO_3P$	2404-03-7	Major impurity, identified in soil[a]
O-Ethyl bis(*N,N*-dimethyl)phosphordiamidate Ethyl tetramethylphosphorodiamidate	$C_6H_{17}N_2O_2P$	2404-65-1	Identified in soil[a]
Bis(*N,N*-dimethyl)phosphoramidocyanidate Tetramethylphosphorodiamidic cyanide	$C_5H_{12}N_3OP$	14445-60-4	Impurity, identified in soil[a]
Bis(ethyl dimethylphosphoramidic) anhydride	NA	NA	Identified in soil[a]
Dimethyl phosphoric ethyl dimethylphosphoramidic anhydride	NA	NA	Identified in soil[a]
Ethyl dimethylphosphoramidic tetramethylphosphorodiamidic anhydride	NA	NA	Identified in soil[a]
Bis(ethyl dimethylamidophosphonyl) dimethylamidophosphonate	NA	NA	Identified in soil[a]
O-Ethyl *N,N*-dimethyl phosphoramidic chloride	NA	2510-93-2	Present in sample
Triethyl phosphate	$C_6H_{15}O_4P$	78-40-0	Identified in soil[a]
Ethyl hydrogen dimethylphosphoramidate	$C_4H_{12}NO_3P$	NA	Identified in soil[a]
Diethyl hydrogen phosphate	$C_4H_{11}PO_4$	NA	Identified in soil[a]
Ethyl dihydrogen phosphate	$C_2H_7PO_4$	NA	Identified in soil[a]
N,N-Dimethylphosphoramidic dichloride	NA	683-85-2	Impurity, identified in soil[a]
Ethyl isopropyl dimethyl phosphoramidate	$C_7H_{18}NO_3P$	NA	Impurity, munitions-grade GA

NA, not available. Data from MacNaughton and Brewer (*27*), Sanches et al. (*34*), D'Agostino et al. (*301,303*), D'Agostino and Provost (*302,305*), and Creasy et al. (*304*).
[a]The compounds were identified in soil contaminated by a leaking container of GA (*302*).

Table 18. Effects of acute exposure to ethyl *N,N*-dimethylphosphoroamidocyanidate (tabun; GA) degradation products, stabilizers, and impurities.

Process/product identification	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
GA hydrolysis			
Dimethylamine (C_2H_7N; 124-40-3)	Rat: oral, 698 mg/kg (*306*) Mouse: oral, 316 mg/kg (*306*) Rabbit: guinea pig, oral 240 mg/kg (*306*) Rat: inhalation, 4,540 ppm/6 hr (*309*) Mouse: inhalation, 7,650 ppm/2 hr; 4,725 ppm/2 hr [(*309*); data from Metzentseva (*310*)]		Human: nose, throat, lung irritation, 100 ppm (*307*) Human: eye, skin, severe burns (*307*) Rabbit: eye, 50 mg/5 min, severe irritation, opacity (*308*) Rat: sensory irritation, RD_{50}, 573 ppm (*309*) Mouse: sensory irritation, RD_{50}, 511 ppm (*309*)
GA products, identified in soil			
Diethyl dimethylphosphoramidate ($C_{10}H_{21}ClNO_3P$; 62484-89-3)	Mouse: IM, 440 mg/kg (*311*)		
Triethyl phosphate ($C_6H_{15}O_4P$; 78-40-0)	Rat: oral, 1,311 mg/kg (*312*) Mouse: oral, 1,500 mg/kg (*314*) Guinea pig: oral, 1,600 mg/kg (*315*) Guinea pig: skin, > 21 g/kg (*312*) Rat: inhalation, > 2,050 mg/m^3/6 hr, 28% respirable aerosol (*312*)	Rat: inhalation, 28,000 ppm/6 hr (*313*)	Rabbit: moderate eye irritation, 100 mg (*312*)

Abbreviations: IM, intramuscular; LC_{50}, median lethal concentration; LC_{LO}, lowest lethal concentration; LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose; RD_{50}, concentration at which a 50% decrease in respiration rate was achieved.

STEL is 15 ppm (*196*). Rothwell et al. (*307*) reported a preliminary chronic inhalation RfC for humans of 2.0 μg/m^3 (1.1 ppb at 25°C and 760 mmHg).

Diethyl dimethylphosphoramidate, a GA product found in soil, also displays moderate acute lethality, as judged by the one value we located. This is an intramuscular LD_{50} value of 440 mg/kg in the mouse (*311*) (Table 18). We found no other information on its toxicity.

The toxicity of another degradation product identified in soil, triethyl phosphate, has been well characterized. It has a low acute toxicity as reflected by LD_{50} and LC_{50} values (Table 18). A more complete review of lethality and other toxicity information is presented in the Chemical Hazard Information Profile for triethyl phosphate (*324*). Triethyl phosphate may have low cholinesterase-inhibiting activity (*323,327*), although Gumbmann and Williams (*328*) suggested that this may be entirely due to tetraethyl pyrophosphate contamination. Triethyl phosphate does not cause delayed neurotoxicity (*329*); however, it does have sedative (narcotic) properties in rats and mice (*327,330*). It is mutagenic in *Drosophila* but not in mammals and has given mixed results with microorganisms (*324*) (Table 19). We found no indication of carcinogenesis testing. Gumbmann et al. (*323*) observed reproductive toxicity at subchronic oral triethyl phosphate doses of 1% and above. Litter size and pup weight were depressed at 1% triethyl phosphate, and 92-day treatment at doses > 1% retarded growth and development such that successful mating was not possible. Doses of 0.1 and 0.5% resulted in mild depression of pup growth. There are currently no occupational standards or recommendations for triethyl phosphate.

Although not unique to GA degradation, cyanide is a major hydrolysis product. The toxicity of cyanide has been well documented. The RfD for cyanide is 0.02 mg/kg/day; an inhalation RfC has not been established (*331*).

Ecotoxicity. GA is highly toxic to aquatic organisms; 20-min LC_{50} values for green sunfish (*Lepomis cyanellus*), fathead minnows (*Pimephales promelas*), and goldfish (*Carassius auratus*) are 0.7, 0.6, and 1.3 mg/L, respectively, as determined by Epstein (*232*). No monitoring data were found for GA in water; unless the source of GA migration to water is continuous, the hydrolysis rate of the agent would limit its presence. No information was located on the toxicity of unique degradation products to aquatic or terrestrial organisms. Dimethylamine is moderately toxic to aquatic organisms, with 24- and 96-hr LC_{50} values for *Daphnia magna* and rainbow trout (*Salmo gairdneri*) of 50 and 120 mg/L, respectively (*205*). Triethyl phosphate is of low toxicity to *Daphnia magna* and fish, with LC_{50} values of > 100 mg/L (*205*). No terrestrial ecotoxicity data were located for GA or for GA degradation products.

GB

The chemical and physical properties of GB, or sarin, are listed in Table 1. GB is a volatile, colorless, and odorless liquid. It is the most volatile of the G agents, with a vapor pressure and volatility of 2.10 mmHg and 22,000 mg/m^3, respectively, thus making it largely a vapor hazard rather than a contact hazard. It is completely miscible with water and, when tactically used on a large scale, could contaminate water sources. GB's toxic mechanism of action, cholinesterase inhibition, is the same as that of VX and the other G agents (*11*).

The Rocky Mountain Arsenal was the only site of GB manufacture in the United States; production took place from 1953 to 1957 (*332*). A Department of Defense inventory of stockpiled material lists GB as being present in projectiles, rockets, and bombs at several U.S. Army depots (*25*). GB is present at approximately 10 nonstockpile military sites in the United States (*230,231*).

Because GB is unstable in the long term, the stabilizers *N,N'*-diisopropyl carbodiimide and/or tributylamine are added to weapons-grade GB (*13,333*). U.S. Army specifications cited by Rosenblatt et al. (*13*) state that *N,N'*-diisopropyl carbodiimide in 1.5% excess is required, and GB must be at least 93% pure, with 0.5% methylphosphonic difluoride as an acceptable component.

Diisopropyl methylphosphonate (DIMP) is a by-product or residue of GB manufacture. It is usually present at 2–3% in isopropyl methylphosphonate waste and is present in sampling wells both on and off the Rocky Mountain Arsenal (*13,334*). In 1974, concentrations of 0.5 μg/L (the limit of detection) to 44,000 μg/L were found in the groundwater near the arsenal (*332*).

Formation of degradation products. GB is considered nonpersistent, as it is volatile, soluble in water, and subject to acidic and basic hydrolysis. The evaporation rate is the same as that of water (*13*). Small (*8*) used a surface deposition model to calculate a volatilization half-life of 7.7 hr for GB. No information on fate in the atmosphere was located, although Kingery and Allen (*28*) stated that nerve agents can be degraded by photolysis and/or radical oxidation. The low calculated Henry's Law constant of 5.4×10^{-7} atm/m^3/mol, based on its high water solubility, indicates slow to essentially no volatilization from water.

Table 19. Carcinogenicity, genotoxicity, reproductive toxicity, and systemic effects of chronic exposure to ethyl *N,N*-dimethylphosphoroamidocyanidate (tabun; GA) degradation products, stabilizers, and impurities.

Degradation product (formula; CAS no.)	Carcinogenicity	Genetic effects	Reproductive effects	Systemic effects
GA hydrolysis				
Dimethylamine (C_2H_7N; 124-40-3)	Rat, mouse: inhalation, negative (tentative) (*307*)	Mutagenicity: *Salmonella*, negative (*222*) Mutagenicity: CHO, negative (*317*) Rat: inhalation, cytogenetic, positive, aneuploidy and chromosome aberrations (*318*) CHO: chromosome aberrations, negative (*317*) CHO: sister chromatid exchange, negative (*317*) Cytogenicity: negative (*319*)	Rat: male, negative, 12 weeks (*316*)	Rats, mice: decreased body weight gain; hematologic changes, inflammation and degeneration of olfactory epithelium (*307*)
GA product, identification in soil				
Triethyl phosphate ($C_6H_{15}O_4P$; 78-40-0)		Mutagenesis: positive, *Drosophila*, multiple doses (*320–322*) Mutagenesis: weakly positive, *Pseudomonas aeruginosa* (*320*) Mutagenesis: mostly negative, *Salmonella*, *Escherichia coli* (*222,324*) Mutagenesis: negative, mouse, dominant lethal test (*325*) *In vitro* transformation: negative, mouse cells (*326*)	Rat: oral, live birth index decrease, 57 g/kg (1% TEP) (*323*)	Rat: oral,120–150 day, increased liver weight, < 10% TEP (*323*) Rat: oral, 120–150 day, increased adrenal weight, 1, 5, and 10% TEP (*323*) Rat: oral, 120–150 day, growth retardation, 5 and 10% TEP (*323*)

Abbreviations: CHO, Chinese hamster ovary; TEP, triethyl phosphate.

The hydrolysis rate of GB in water is temperature, pH, and water quality dependent (*9,28,44,335*). As indicated in Table 20, breakdown of GB results in only a few degradation products; according to Rosenblatt et al. (*13*), these are relatively nontoxic. Hydrolytic half-lives are shorter in acidic and basic solutions than at a neutral pH. At 20°C and the pH of natural waters where the half-life is a minimum, estimates of the half-life range from 461 hr (pH 6.5) to 46 hr (pH 7.5) (*9*). At 25°C, the half-life ranges from 237 hr (pH 6.5) to 24 hr (pH 7.5). A half-life of 8,300 hr at 0°C and pH 6.5 indicates some persistence at low temperatures. The hydrolysis products are acids (Table 20), and their presence increases the rate of hydrolysis (*13*). The rate of hydrolysis under natural conditions is accelerated by the presence of ions in solution. Metal cations such as copper and manganese in seawater also increase the rate of hydrolysis (*335*).

GB hydrolyzes first through the loss of fluoride, producing IMPA and hydrofluoric acid, and second, more slowly through the loss of the isopropanol to produce MPA (*13,27,28*). The same products are produced under acidic conditions (Figure 4). According to Clark (*9*), alkaline hydrolysis would result in isopropanol, methylfluorophosphonic acid and, with the loss of fluoride, MPA. This pathway has not been confirmed in other studies.

The fate of GB in soil includes hydrolysis, evaporation, and leaching; the phosphonic acid hydrolysis products are subject to biodegradation. Small (*8*) reviewed studies of the stability of GB in soil and concluded that ≥ 90% of GB added to soil is lost in the first 5 days. GB is more persistent at low temperatures (*34,43*). Droplets of GB deposited on the snow surface under actual field conditions in Norway were removed by a combination of evaporation and hydrolysis (*42,43*). Within 5 hr, approximately 55% was removed by evaporation and 15% was removed by hydrolysis. Newly fallen snow protected droplets from evaporation; GB was still present 2 and 4 weeks after being sprayed on the snow. The hydrolysis product IMPA and several impurities such as DIMP were present up to 4 weeks later (*42,43*). After application of 10 mg GB over a 10 × 10 m area of moss (temperature 2.5–8°C, humidity 60–100%, wind speed 1–10 m/sec), detectable concentrations [≥ 1 pg/dm^3 (≥ 1 ng/m^3)] were found in the air for 9 days (*34*). Small (*8*) pointed out that GB degradation products sorb to soil depending on the soluble organic carbon content of the soil.

Although no direct information is available on biodegradation of the nerve agents in soil, enzymes capable of hydrolyzing organophosphorus esters, including some nerve agents, have been isolated from bacteria (*29*). However, the toxicity of these agents probably precludes direct biodegradation. All four nerve agents degrade to alkyl methylphosphonates by a variety of other mechanisms and then, slowly, to MPA (with the likely exception of GA).

Additional information on the environmental fate of several degradation products was available. Chemically, IMPA is extremely stable; Rosenblatt et al. (*5*) predicted a half-life of over 1,900 years. As previously noted, hydrolysis of IMPA produces MPA and isopropyl alcohol. A low vapor pressure for IMPA, 0.0034 mmHg at 25°C (*8*), makes it unlikely that atmospheric contamination will take place. A water solubility of 48 g/L and a low K_{oc} of 12 (*8*) indicate a high potential for migration to groundwater. The pK_a values of 1.98 (*8*) and 2.38 (*260*) indicate that IMPA will be in the ionized state in water. IMPA is a known contaminant of groundwater in the Rocky Mountain Arsenal area and has been detected in both soils and water at five U.S. Army installations (*28*). The fate of MPA in the environment was discussed in the section on VX. As noted, MPA is stable in the environment and leaches through soils.

IMPA is relatively resistant to bacterial degradation. However, some strains such as *Pseudomonas testosteroni* are capable of metabolizing IMPA and MPA (*8,336*). Several strains of bacteria isolated from sewage samples, including *P. testosteroni*, were capable of using MPA as a phosphorus source but not as a carbon source (*8*). *P. testosteroni* was also capable of metabolizing IMPA (via cleavage of the C–P bond) to methane and an inorganic phosphorus compound (*336*).

Because of its low volatility, DIMP is not likely to be found in the air above contaminated areas; also, volatilization from water should be insignificant (*337*). DIMP is miscible with water (*338*) and was stable for months when added to water; there was no significant loss of DIMP from the water column to the atmosphere (*339*). DIMP in distilled water was stable during a 232-hr period of irradiation with a mercury lamp (*340*). However, Bentley et al. (*341*) reported that DIMP solutions allowed to age for 96 hr before testing were 50% less toxic to fish, indicating degradation. A log K_{ow} of 0.478 (*342*) indicates little potential to bioconcentrate in organisms. As previously noted, DIMP is a groundwater contaminant in the area of manufacture at the Rocky Mountain Arsenal (*332*). Its release to groundwater at this site represents the largest known release of any CW agent-related compound to the environment; it is expected that other findings of CW contamination within the United States would be small by comparison.

DIMP in soil biodegrades slowly. When radiolabeled DIMP was applied to soil, 13.4% evolved as $^{14}CO_2$ after 34 weeks (*340*). In another study, 6.0 and 6.4% of DIMP evolved as $^{14}CO_2$ from previously contaminated and uncontaminated soils obtained from the Rocky Mountain Arsenal (*343*). Most of the activity recovered from the soil was in the form of the parent compound. The concentration of DIMP in five soil samples from the Rocky Mountain Arsenal ranged from < 0.05 to 0.24 mg/kg (*343*). The half-life of DIMP on the soil surface after airborne deposition was between 26 and 28 days (*339*). For foliar surfaces, the half-life was calculated at 3.6–4.2 days.

Table 20. Degradation products, impurities, and stabilizers of isopropyl methylphosphonofluoridate (sarin; GB).

Name/synonym	Formula	CAS no.	Source
Isopropyl methylphosphonic acid (IMPA)	$C_4H_{11}PO_3$	1832-54-8	Hydrolysis of GB
Methylphosphonic acid (MPA)	CH_5PO_3	993-13-5	Hydrolysis of GB
Diisopropyl methylphosphonate (DIMP)	$C_7H_{17}PO_3$	1445-75-6	Impurity
Methylphosphonic difluoride	CH_3F_2OP	676-99-3	Potential impurity
Diisopropyl carbodiimide (DIPC)	$C_7H_{14}N_2$	693-13-0	Stabilizer
N,N'-Diisopropylurea	$C_7H_{16}N_2O$	4128-37-4	Hydrolysis of diisopropyl carbodiimide
Tributylamine (TBA)	$C_{12}H_{27}N$	102-82-9	Stabilizer
n-Butanoic acid	$C_4H_8O_2$	107-92-6	Decontamination product of tributylamine
Dibutylchloramine	$C_8H_{18}ClN$	999-33-7	Stabilizer

Data from Small (*8*), Rosenblatt et al. (*13*), MacNaughton and Brewer (*27*), and Sanches et al. (*34*).

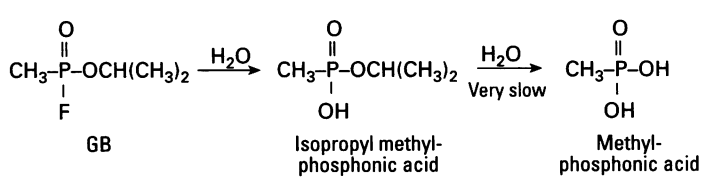


Figure 4. Primary hydrolysis pathway of isopropyl methylphosphonofluoridate (sarin; GB) in the environment.

Results of soil lysimeter studies indicate that DIMP moves through soil with irrigation water, whereas most of the compound is retained in dry soils (*344*). Radioactive DIMP at a concentration of 20 ppm was mixed with columns containing dry or wet soil. Air was passed across the surface for extended periods. At the end of 250 hr, the dry soil had retained over 95% of its radioactivity and the moist soil columns retained 78% of the initial radioactivity, indicating little evaporation. A pK_a for DIMP was not found.

Few data were located on other degradation products or stabilizers. Methylphosphonic difluoride rapidly hydrolyzes to MPA and hydrogen fluoride (*13*). The vapor pressure of methylphosphonic difluoride at 19.5°C is 27 mmHg and the specific gravity is 1.36 (*345*). Hydrolysis of diisopropyl carbodiimide produces *N,N'*-diisopropylurea. Tributylamine is resistant to hydrolysis and is not expected to volatilize (*13*).

Decontamination. Because of its rapid evaporation, large-scale decontamination for GB is unnecessary (*234*). Decontamination of GB with aqueous acidic or alkaline solutions results in hydrolysis to the same products discussed previously, but at a much more rapid rate (*13,346*). For example, at a temperature of 24.5°C and a pH of 6, the half-life of GB (2×10^{-4} M), in the presence of hypochlorite from sodium hypochlorite or $Ca(OCl)_2$ (2.8×10^3 M), was approximately 11 min (*347*). In hypochlorite solutions, which are fairly alkaline, GB would be hydrolyzed with a half-life of < 1 sec (*13*). The half-life for GB with DS-2 is < 30 sec. Reaction with DS-2 or STB produces IMPA and fluoride ion (*8*). Detoxification by Fichlor is predicted to be slow (*29*). G-agents do not react with chlorine dioxide and several other decontaminants (*13*).

Alkyl methylphosphonic acids such as IMPA are extremely resistant to basic hydrolysis but are slowly hydrolyzed under acid conditions and elevated temperatures to MPA (*28*). IMPA and MPA can be oxidized to phosphoric acid, carbon dioxide, and water in the presence of hydrogen peroxide, oxygen, and UV light (*265*). Mill and Gould (*265*) found no intermediates in the oxidation of MPA, but acetone, acetic acid, and MPA were formed in the oxidation of IMPA.

Table 21. Effects of acute exposure to isopropyl methylphosphonofluoridate (sarin; GB) degradation products, stabilizers, and impurities.

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
GB hydrolysis			
Isopropyl methylphosphonic acid (IMPA) ($C_4H_{11}O_3P$; 1832-54-8)	Rat: oral, male, 7,650 mg/kg (*349*) Rat: oral, female, 6,070 mg/kg (*349*) Mouse: oral, male, 5,620 mg/kg (*349*) Mouse: oral, female, 6,550 mg/kg (*349*)		Rabbit: negative, eye irritant, 100 mg (*349*) Rabbit: mild skin irritant, 2 g/kg/24 hr (*349*)
Methylphosphonic acid (MPA) (CH_5O_3P; 993-13-5)	Rat: oral, 5,000 mg/kg (*273*) Mouse: oral, > 5,000 mg/kg (*273*)		Human: skin and eye irritant (*274*)
GB impurities			
Diisopropyl methylphosphonate (DIMP) ($C_7H_{17}PO_3$; 1445-75-6)	Rat: oral, 826 mg/kg (*350*) Mouse: oral, 1,041 mg/kg (*350*) Mink: oral, 503 mg/kg (*334*) Duck: oral, 1,490 mg/kg (*334*) Cattle: oral, ~ 750 mg/kg (*351*)		Draft ATSDR Toxicological Profile (*337*); examples follow: Rat: ataxia, decreased activity; prostration, 430 mg/kg LOAEL (*350*) Mouse: decreased activity; prostration, 430 mg/kg LOAEL (*350*) Mink: salivation, lethargy; immobilization, 300 mg/kg LOAEL (*334*)
Methylphosphonic difluoride (CH_3F_2OP; 676-99-3)	Mouse, dog: inhalation, 2,700 mg/m^3/30 min (*345*) Rat: inhalation, 8,100 mg/m^3/30 min (*345*) Monkey: inhalation, 3,000 mg/m^3/30 min (*345*) Guinea pig: inhalation, < 1,600 µg/L/1 hr (mg/m^3) (*352*)		Rat, mouse, dog, monkey: eye irritation (*345*) Rat, dog, monkey: corneal opacity, haze (*345*) Mouse: muscle weakness, ataxia (*345*) Dog, monkey: miosis (*345*) Rat, mouse, guinea pig: respiratory distress (*345,352*) Dog: pulmonary edema, congestion (*345*)
GB decontamination			
Isopropyl methylphosphonic acid (IMPA) ($C_4H_{11}O_3P$; 1832-54-8)	Rat: oral, male, 7,650 mg/kg (*349*) Rat: oral, female, 6,070 mg/kg (*349*) Mouse: oral, male, 5,620 mg/kg (*349*) Mouse: oral, female, 6,550 mg/kg (*349*)		Rabbit: negative, eye irritant, 100 mg (*349*) Rabbit: mild skin irritant, 2 g/kg/24 hr (*349*) Human: severe eye irritant, temporary blindness (*284*)
GB stabilizers and decontamination products			
Diisopropylcarbodiimide (DIPC) ($C_7H_{14}N_2$; 693-13-0)	Mouse: intravenous, 36 mg/kg (*283*)		
Tributylamine ($C_{12}H_{27}N$; 102-82-9)	Rat: oral, 740 mg/kg (*353*) Rat: oral, 540 mg/kg (*354*) Mouse: oral, 114 mg/kg (*355*) Rabbit: oral, 615 mg/kg (*355*) Guinea pig: oral, 350 mg/kg (*355*) Rabbit: skin, 250 µL/kg (194 mg/kg) (*354*)	Rat: inhalation, 75 ppm/4 hr (*354*)	Human: central nervous system stimulation, skin irritation, sensitization (*14,240*) Human: eye, skin, and respiratory irritant (*356*)
n-Butanoic acid[a] ($C_4H_8O_2$; 107-92-6)	Rat: oral, 2 g/kg (*127*) Rabbit: skin, 530 mg/kg (*360*)	Human: skin, 1%/48 hr (*357*) Mouse: oral, 500 mg/kg (*361*)	Human: eyes, skin, respiratory tract, severe irritant (*358,359*) Rabbit: skin, severe irritation, 10 mg/24 hr (*70*) Rabbit: skin, moderate irritation, 500 mg (*360*) Rabbit: eye, severe irritation, 250 µg (*70*)

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; LC_{50}, medial lethal concentration; LC_{LO}, lowest lethal concentration; LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose; LOAEL, lowest-observed-adverse-effect level.
[a]Decontamination product of GB stabilizer tributylamine.

The impurity methylphosphonic difluoride rapidly hydrolyzes to MPA, especially at a high pH (*13*). Dialkylmethylphosphonates such as DIMP undergo slow basic hydrolysis to salts of alkyl methylphosphonic acids. Although tributylamine is resistant to hydrolysis, it can be oxidatively dealkylated to dibutylamine and butyraldehyde (butanal) by hypochlorite (*13*). Initial reaction products with STB are butyraldehyde and dibutylchloramine; butyraldehyde oxidizes to *n*-butanoic acid (butyric acid) in alkaline solution with hypochlorite (*8*).

Acute and chronic mammalian toxicity. GB hydrolyzes to IMPA, which slowly undergoes further hydrolysis to the very stable MPA. The toxicity of MPA was discussed previously as a product of VX hydrolysis (Table 15). IMPA also forms in the course of GB decontamination using either STB or DS-2 solutions. IMPA possesses low oral toxicity in rats and mice (*348*) (Table 21). Mecler (*349*) reported that it produced only mild skin irritation and no eye irritation in rabbits. The author also determined that IMPA did not induce delayed hypersensitization in guinea pigs (*349*) (Table 22). In subchronic (90-day) toxicity tests of IMPA in drinking water of rats, no adverse effects were observed on any of a variety of end points at any dose tested; the highest actual intakes were 293 and 406 mg/kg/day in males and females, respectively (*349*). The target doses were 300, 1,000, and 3,000 ppm; water intake was measured and average IMPA intakes were 31, 119, and 350 mg/kg/day for male and females combined [calculated from Mecler (*349*)]. Similarly, mutagenicity testing with and without metabolic activation in *Salmonella typhimurium* gave negative results (*349*). No indication of carcinogenicity testing or testing for reproductive effects appeared in the literature searches. Confidence in the low toxicity of IMPA further derives from studies of DIMP, which is > 90% metabolized to IMPA within 24 hr in mammalian species and has demonstrated low acute and negligible chronic and reproductive toxicity (*337,363*).

The U.S. EPA has calculated an oral RfD for IMPA of 0.1 mg/kg/day based on the male rat NOAEL of 3,000 ppm (exposure via drinking water) and an uncertainty factor of 3,000 (*369,370*). From the oral RfD, the U.S EPA derived an adult lifetime drinking water health advisory value of 0.7 mg/L (*369,371*). There is no standard for occupational exposure.

The GB contaminant DIMP is fairly stable in the environment and has been detected in the soil, surface water, and groundwater at the Rocky Mountain Arsenal (*337*). Data on its toxicity are available for a

Table 22. Carcinogenicity, genotoxicity, reproductive toxicity, and systemic effects of chronic exposure to isopropyl methylphosphonofluoridate (sarin; GB) degradation products, stabilizers, and impurities.

Degradation product (formula; CAS no.)	Carcinogenicity	Genetic effects	Reproductive effects	Systemic effects
GB hydrolysis				
Isopropyl methylphosphonic acid (IMPA) ($C_4H_{11}PO_3$; 1832-54-8)		Mutagenicity: *Salmonella*, negative (*349*)		No toxicity to rats fed 300 ppm in water for 90 days (*349*)
GB impurity				
Diisopropyl methylphosphonate (DIMP) ($C_7H_{17}PO_3$; 1445-75-6)		Mutagenicity: *Salmonella*, negative, (± S9) (*362*) Mutagenicity: *S. cerevisiae*, negative (*362*)	Mink: oral, negative, two-generation study (*363*) Rat: oral, negative, three-generation study (*362*) Mink: oral, negative, one-generation study (*334*)	Mink: mild hematologic effects (*363*) Guinea pig: dermal hypersensitivity, negative (*350*)
GB decontamination				
Isopropyl methylphosphonic acid[a] (IMPA) ($C_4H_{11}O_3P$; 1832-54-8)		Mutagenicity: *Salmonella*, negative (*349*)		No toxicity to rats fed 300 ppm in water for 90 days (*349*)
GB stabilizer DIPC, decontamination				
Chloroform[b] ($CHCl_3$; 67-66-3)	Probable human carcinogen (*142,143*) Rat: positive (*87*) Mouse: positive (*87*) Rat: positive, mouse: negative (*150*)	Mutagenicity: Ames, negative (*144*) Mutagenicity: yeast, positive (*146*) Mutagenicity: mouse, positive (*145*) Chromosome effects: human lymphocytes, negative (*151*) SCE: *in vitro*, low or negative (*152–154*) SCE: mouse, *in vivo*, positive (*154*) Micronucleus: negative (*155*) Delayed cell cycle: human lymphocytes, positive (*154*)	Rat: fetotoxic, retarded development, teratogenic (*145*) Mouse: sperm abnormalities (*147*) Mouse: negative in sperm morphology assay (*149*)	Human: hepatomegaly, fatty liver degeneration, toxic hepatitis (*87*) Human: central nervous system, psychiatric, neurologic effects (*148*)
GB stabilizer TBA, decontamination				
Tributylamine ($C_{12}H_{27}N$; 102-82-9)		Mutagenicity: negative, *Salmonella* (*222*)		
n-Butanoic acid[c] ($C_4H_8O_2$; 107-92-6)	Negative (as promoter) (*364*)	Mutagenicity: negative *Salmonella* (*319*) Chromosome aberrations: negative, Chinese hamster lung cells (*319*) Sister chromatic exchange: positive[d] (*366*) Human: HeLa cell; chicken fibroblasts, positive, DNA synthesis inhibition (*367*) Human: lymphocyte, positive, DNA synthesis inhibition (*368*)	Developmental defects, *Xenopus* embryos (*365*)	

Abbreviations: DIPC, diisopropylcarbodiimide; TBA, tributylamine.
[a]Isopropyl methylphosphonic acid may be formed by GB decontamination with either supertropical bleach or decontamination solution 2 (diethylenetriamine, 2-methoxyethanol, and sodium hydroxide). [b]Chloroform is a possible product of diisopropylcarbodiimide reaction with supertropical bleach. [c]*n*-Butanoic acid is a possible product of tributylamine reaction with supertropical bleach. [d]Also reversible inhibition of cell proliferation and differentiation in Chinese hamster lung cells (*366*).

number of mammalian species and for a variety of end points. As mentioned above, DIMP is rapidly metabolized to IMPA in mammals and, like IMPA, has demonstrated rather low toxicity (Table 21). Unlike IMPA, DIMP has been studied in a number of species, including rat, mouse, dog, cow, mink, and duck. Oral LD_{50} values range from approximately 500 to 1,400 mg/kg in mammalian species; it is ~1,500 mg/kg in ducks. Neurotoxicity, as manifested by ataxia (rat, cow), decreased activity (rat, mouse), prostration (rat, mouse, cow, mink), salivation (mink, duck), and depression and engorgement of meningeal vessels along with excess fluid in cerebral ventricles (cow), is the predominant result of acute exposure to doses in the moderate-to-lethal range (*337*). However, DIMP is not a strong cholinesterase inhibitor. Slight-to-modest depression of plasma cholinesterase resulted from subchronic or chronic exposure of mink to DIMP in food (*363,372*). The degree of cholinesterase inhibition was indicative of exposure but not sufficient to be considered an adverse effect (*337,363*). Red blood cell cholinesterase was not affected. Aulerich et al. (*334*) observed slight indicators of hematologic effects in juvenile pastel mink (decreased hematocrit); others saw evidence of mild hemolysis in dark brown mink (decreased hematocrit, hemoglobin, and increased red blood cell Heinz body inclusions) dosed subchronically (*372*) and chronically (*363*).

Hart (*362*) reported no evidence of reproductive or developmental toxicity in a three-generation study of DIMP. Furthermore, Aulerich et al. (*334*) found no evidence of reproductive toxicity in mink and Bucci et al. (*363*) obtained no evidence of reproductive toxicity in a more carefully controlled two-generation study. Aulerich et al. (*334*) reported the occurrence of maternal deaths that were apparently dose related. However, some of the deaths occurred in the period between mating and lactation (*337*), and most or all may have resulted from nursing or stress syndrome, a syndrome unique to mink. Bucci et al. (*363*) attributed some deaths to this stress syndrome in their two-generation study. The Aulerich et al. study (*334*) also involved evaluation of a second chemical (dicyclopentadiene), and deaths were also observed in those animals. Attribution of the deaths in the DIMP portion of the study to DIMP toxicity appears questionable, especially in light of the results of Bucci et al. (*363*).

The limited data available on genotoxicity indicate that DIMP is not mutagenic to *S. typhimurium*, with or without metabolic activation, nor does it cause gene mutations in *Saccharomyces cerevisiae* (*362*) (Table 22). No data regarding DIMP carcinogenicity in humans are available. Although no lifetime carcinogenicity studies have been conducted in mice or rats (*373*), the recent study of Bucci et al. (*363*) included F_1 animals dosed for 12–13 months. The authors observed no gross or microscopic indicators of treatment-related neoplastic or preneoplastic lesions. The lack of DIMP-induced *in vitro* genotoxicity suggests a low potential for carcinogenicity.

Guidelines and regulations applicable to DIMP are summarized in the Agency for Toxic Substances and Disease Registry (ATSDR) draft toxicologic profile for DIMP (*337*). The U.S. EPA calculated a reference dose of 0.08 mg/kg/day based on a NOAEL of 75 mg/kg/day in a 90-day study of dietary exposure of dogs (*362*) and appropriate uncertainty factors. The corresponding lifetime drinking water health advisory for DIMP determined by the U.S EPA on the basis of this RfD is 600 µg/L (*371*). However, the state of Colorado has promulgated groundwater and surface water standards of 8 µg/L on the basis of a LOAEL of 11 mg/kg/day for lethality to female mink reported by Aulerich et al. (*334*) and several uncertainty factors (*374,375*). No occupational standards or guidelines have been identified for DIMP

The vapor of the GB precursor and contaminant methylphosphonic difluoride is extremely irritating to eyes, nasal passages, and airways (*345*). Whole-body inhalation studies in rats, mice, dogs, and monkeys indicated lethality about 150–1,100 times less than that of GB (*345*) (Table 21). Rats were the least susceptible and mice the most susceptible; dogs and monkeys were almost as sensitive as mice to the toxic effects of methylphosphonic difluoride. Dahl et al. (*352*) reported that guinea pigs were more sensitive to this substance than rats. Animals exposed to methylphosphonic difluoride exhibit signs consistent with anticholinesterase activity; these signs include gasping, muscle weakness, and ataxia in mice; gasping in a few rats; gasping, salivation, and miosis in dogs; and gasping, salivation, rhinorrhea, and miosis in monkeys (*345*). Dahl et al. (*352*) stated that methylphosphonic difluoride hydrolyzes rapidly under physiologic conditions to hydrogen fluoride and methylphosphonofluoride acid (MF); the latter hydrolyzes to MPA (*13*). The oral toxicity of a mixture of methylphosphonic difluoride hydrolysis products in rats was similar to that of the fluoride ion ($LD_{50} \cong$ 100 mg/kg), whereas the toxicity of MF alone was not as great ($LD_{50} \cong 300$ mg/kg); the associated symptoms of MF intoxication were quite different from those produced by the fluoride ion (*352*). The fact that the toxicity of the hydrolysis product mixture was essentially the same as that of the fluoride ion is further evidence for the lack of MPA toxicity. Genotoxicity and chronic toxicity data are lacking for methylphosphonic difluoride. There are no environmental guidelines or occupational standards or recommendations for this compound.

Either of two stabilizers were added to GB, diisopropylcarbodiimide or tributylamine. The former was also used with VX; thus, diisopropylcarbodiimide and its degradation products are discussed in the section on VX (Tables 15 and 16). Tributylamine is moderately toxic by acute oral exposure (Table 21). Only one data point is available for dermal toxicity. Little is known about the chronic toxicity of tributylamine; it tested negative for mutagenicity in *Salmonella* (*222*) (Table 22). Species-specific comparisons of oral LD_{50} data show tributylamine to be about 0.2–0.4% as lethal as GB (*228*). It is about 13% as toxic as GB to the rabbit by dermal exposure [calculated from U.S. Army GB data (*228*)]. Tributylamine causes eye, skin, and respiratory irritation in humans (*356*) as well as CNS stimulation and skin sensitization (*14*). No environmental guidelines or occupational standards or recommendations for tributylamine were located. Degradation products associated with decontamination of tributylamine differ depending on the decontaminant used. Tributylamine does not react in the presence of DS-2; with STB, it produces dibutylchloramine and *n*-butanoic acid (*8*). No biologic data were found for dibutylchloramine.

n-Butanoic acid is a severe irritant for human eyes, skin, and respiratory tract (*358,359*) (Table 21). It is also corrosive (*376*). *n*-Butanoic acid can cause mild-to-severe skin or eye irritation in rabbits depending on the dosage and mode of exposure (*70,360*). This organic acid has low oral toxicity in rats and moderate toxicity in rabbits following dermal exposure. In humans, an estimated LD_{LO} for dermal exposure is 1% for 48 hr (*357*). *n*-Butanoic acid has shown no activity as a promoter of carcinogenesis (*364*); it did not induce mutations in the Ames test or chromosome aberrations *in vitro* (*319*) (Table 22). However, it did induce a 3- to 4-fold increase in SCE and reversible inhibition of cell proliferation and differentiation in Chinese hamster lung cells (*366*). *n*-Butanoic acid inhibits DNA synthesis in human HeLa cells (*367*) and human lymphocytes (*368*). Dawson (*365*) showed that it induced developmental defects in frog (*Xenopus* sp.) embryos. It should be noted that *n*-butanoic acid is a natural ingredient of foods (*14*).

Ecotoxicity. During short exposures at a neutral pH where hydrolysis is at a minimum, GB is highly toxic to fish species, with

LC_{50} values of < 1 mg/L. For example, the 24-hr LC_{50} of GB for green sunfish was 0.002 mg/L; at a constant pH of 8, the LC_{50} was 0.0095 mg/L (*232*).

Aquatic toxicity data are available for only two degradation products, MPA and DIMP. The data for MPA (*273*) were discussed in the section on VX.

The toxicity of DIMP to several wildlife species was studied by Aulerich et al. (*334*). LD_{50} values for adult mallard ducks, bobwhite quail, and mink were 1,490, 1,000, and 503 mg/kg, respectively. The mink study (*334*) was discussed in the section on mammalian toxicity. When 12-day-old mallard ducklings were fed up to 16,000 ppm DIMP in the diet for 5 days, no mortality occurred (*334*). Feed consumption and body weight gains were reduced during the treatment period. At autopsy, no pathologic changes were noted. Aulerich et al. (*334*) calculated the dose to be 2,060 mg/kg/day. Female adult mallard ducks exposed to dietary concentrations of 1,000, 3,200, or 10,000 ppm DIMP for 10 weeks before onset of egg laying and throughout the reproductive cycle did not have decreased feed consumption or decreased body weight gain. Only hens that received 10,000 ppm had a decrease in egg production. There were no differences in hatchability or survival of the young between controls and any treated group (*334*).

Aulerich et al. (*334*) fed groups of 14-day-old bobwhite quail 0, 4,000, 8,000, 12,000, 16,000, 20,000, 24,000, 28,000, 32,000, or 36,000 ppm DIMP in the diet for 5 days. Mortality occurred in the groups administered 24,000 and 28,000 ppm (60 and 10%, respectively), but not in any other group. Feed consumption and body weight gain were reduced in the higher exposure groups, but no pathologic changes were observed at autopsy. The 36,000 ppm diet delivered a dose of 4,983 mg/kg/day. In a chronic study, DIMP was fed to adult bobwhite quail for 30 weeks. Initial levels were 0, 1,200, 3,800, and 12,000 ppm in the diet, but because of mortality in the 3,800 and 12,000 ppm groups, the dietary levels were reduced to 380 ppm after 26 days (3,800 ppm dietary level) and to 0 ppm after 18 days (12,000 dietary level). The 1,200 ppm and adjusted 3,800 and 12,000 ppm dietary levels had little affect on survival and reproduction (*334*).

Bentley et al. (*341*) tested the toxicity of DIMP to algae (*Microcystis aeruginosa, Anabaena flos-aquae, Selenastrum capricornutum,* and *Navicula pelliculosa*), invertebrates [water flea (*Daphnia magna*), midge (*Chironomus tentans*), scud (*Gammarus fasciatus*), and sowbug (*Ascellus militaris*)], and fish [bluegill (*Lepomis macrochirus*), channel catfish (*Ictalurus punctatus*), and fathead minnow (*Pimephales promelas*)]. The most sensitive species tested was bluegill sunfish, with a 96-hr LC_{50} of 257 mg/L at 25°C. Van Voris et al. (*339*) reported that DIMP had no significant effect on the growth of *Chlorella pyrenoidosa* or *S. capricornutum* at concentrations up to 500 mg/L. The LD_{50} for earthworms (*Eisenia fetida*) was 1,500 µg/g soil (*339*). Soil microbial activity as indicated by dehydrogenase activity was reduced by DIMP at mass loading rates of 300–3,000 µg/cm^2 (*339*).

Concentrations of 10 and 100 ppm of DIMP in hydroponic solutions were phytotoxic (signs of leaf burn or leaf necrosis) to test plant species (bean, radish, wheat, tomato, sugar beet, meadow fescue, and rose). After 44 days, juniper, corn, and carrot were unaffected at 100 ppm (*344*). In soil studies, an irrigation-water concentration of 20 ppm DIMP was a no-effect level for the tested species and 50 ppm was an effect level for phytotoxicity. Bioconcentration from both soil and hydroponic solutions took place, with the highest concentrations in the plant leaves. Bioconcentration for the different species was ≤ 20 (*344*). DIMP at application rates of 1–40 µg/cm^2 caused severe damage to tall fescue and defoliation of short-needle pine; however, new growth was initiated within 21 days postexposure (*339*).

GD

The chemical and physical properties of GD, or soman, are listed in Table 1. GD is a colorless liquid that gives off a colorless vapor with a fruity odor. Its volatility, intermediate between that of GA and GB, is high enough to make it a vapor hazard. It is less water soluble and more lipid soluble than the other G agents, which results in more rapid skin penetration and greater toxicity (*11*). Thickeners such as methyl methacrylate are added to GD to increase persistence (*27*).

Little information was located on the production and storage of GD. Although it was a significant part of the former Soviet Union's chemical arsenal and large quantities were produced there during the cold war, GD is not part of the U.S. unitary stockpile; it is likely that only research quantities are available in the United States. Survey and analyses reports of nonstockpile materiel sites indicate that GD might be present at Dugway Proving Ground (*230,231*).

Formation of degradation products. GD is less volatile than GB, evaporating at one-fourth the rate of water (*13*). The added thickeners retard evaporation. The vapor pressure and volatility at 25°C are 0.40 mmHg and 3,900 mg/m^3, respectively (*11*). Assuming that its structure is similar to that of GB and using a surface deposition model, GD is expected to volatilize with a half-life of ~ 7.7 hr (*8*). Volatilization rates calculated using a bulk soil model were three orders of magnitude slower than those obtained using the surface deposition model. A calculated Henry's Law constant of 4.6×10^{-7} indicates that some volatilization from water may occur.

Like the other G agents, GD is subject to hydrolysis, but the rate of hydrolysis is slow under neutral conditions (*29*). GD hydrolyzes first through the loss of fluoride, and second, more slowly through the loss of the alkoxy group. Thus, the primary hydrolysis product is pinacolyl methylphosphonic acid, which slowly hydrolyzes, with the release of pinacolyl alcohol, to MPA (Figure 5) (*9,27,28*). Qualitatively, the hydrolysis of GD is similar to that of GA; however, the reaction rate is five times slower than that of GA, and GD has an estimated half-life of approximately 60 hr at pH 6 and 25°C (*377*). The reaction is both acid and base catalyzed, resulting in a hydrolysis curve similar to that of GA (*9*). At a pH > 10, hydrolysis to pinacolyl methylphosphonic acid occurs within a few minutes (*29*). Because an acid is produced, the pH decreases, lessening the rate of hydrolysis. However, this effect is small in the environment and in the normal case of decontamination in which excess decontaminant is added. GD stored at pH 6 for 8 weeks had a pinacolyl methylphosphonic acid/MPA ratio of 250 (*377*), which Kingery and Allen (*28*) extrapolated to a half-life of 27 years. The C–P bond is very resistant to hydrolysis. Hydrolysis products and impurities are listed in Table 23.

No data were found on the fate of pinacolyl methylphosphonic acid or pinacolyl alcohol in the environment. Like alkyl methylphosphonic acids, pinacolyl methylphosphonic acid is probably resistant to hydrolysis. A pK_a of 2–2.5 (*28,260*) indicates that pinacolyl methylphosphonic acid will be present as an anion at environmental pHs. Johnsen and Blanch (*43*) noted that

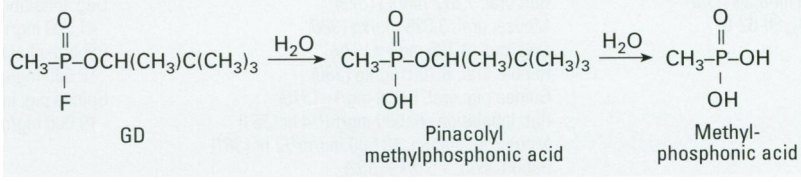


Figure 5. Primary hydrolysis pathway of pinacolyl methylphosphonofluoridate (soman; GD) in the environment.

the impurity diisopropyl methylphosphonate was relatively stable in a cold environment, as evidenced by its recovery 4 weeks after the deposition of GD on snow.

Decontamination. As noted above, hydrolysis is both acid and base catalyzed and is essentially complete in 5 min in a 5% sodium hydroxide solution (*11*). Copper and imidazole accelerate GD hydrolysis (*28*). Studies reviewed by Kingery and Allen (*28*) demonstrate the difficulty of dealkylation of alkyl methylphosphonates in water and the stability of the C–P bond.

Acute and chronic mammalian toxicity. Hydrolysis products of GD include pinacolyl methylphosphonic acid and MPA. No biologic data were located for pinacolyl methylphosphonic acid or the impurity dipinacolyl methylphosphonate. Toxicologic information for MPA was discussed above in the "VX" section (Table 15).

Methyl methacrylate is used as a thickener for GD. This substance is an eye, skin, and mucous membrane irritant in humans (*157*) and animals (*378,379*) (Table 24). It also causes allergic contact dermatitis in humans (*157*) and hypersensitization in guinea pigs (*383*). Occupational exposures have resulted in complaints of headache, fatigue, sleep disturbance, irritability, loss of memory, and pain in the extremities (*157*). Animal studies have shown that methyl methacrylate can cause CNS depression, hypotension, liver and kidney toxicity, and respiratory arrest (*157,379*). Methyl methacrylate in surgical bone cement has caused episodes in humans of hypotension followed by cardiac arrest and at least one fatality (*157*).

Methyl methacrylate has produced mixed results in genotoxicity assays (Table 25). It did not induce mutations in the Ames test (*157,222*), although it gave positive results in mouse lymphoma cells (*394,395*). Methyl methacrylate has given positive results for SCE and weakly positive indications for chromosome aberrations (*384,391,396*), but was negative for sex-linked recessive lethal mutations in *Drosophila* and weakly positive or equivocal for micronucleus induction (*391*). Two-year inhalation studies in rats and mice gave no evidence of carcinogenicity (*384*). A 2-year drinking water study in rats was also negative for carcinogenicity (*388*); however, local tumors may be formed at the site of methyl methacrylate implants; the International Agency for Research on Cancer considers methyl methacrylate not classifiable with regard to human carcinogenicity (*157*). Methyl methacrylate appears not to be teratogenic but has shown embryo- and fetotoxicity on maternal inhalation exposure (*157,386*).

The OSHA PEL and ACGIH TLV-TWA for methyl methacrylate are both 100 ppm (410 mg/m^3) (*196,197*). A chronic RfD of 0.08 mg/kg/day has been calculated, based on a NOEL of 7.5 mg/kg/day during a 24-month oral exposure of rats and the end point of increased relative kidney weight (*388*) together with an uncertainty factor of 100 (*397*).

Ecotoxicity. No data were located on the ecotoxicity of GD.

Table 23. Degradation products, impurities, and thickener of pinacolyl methylphosphonofluoridate (soman; GD).

Name	Formula	CAS no.	Source
Pinacolyl methylphosphonic acid	$C_7H_{17}O_3P$	616-52-4	Hydrolysis of GD
Methylphosphonic acid	CH_5O_3P	993-13-5	Hydrolysis of GD
Pinacolyl alcohol	$C_6H_{14}O$	464-07-3	Hydrolysis of pinacolyl methylphosphonic acid
Dipinacolyl methylphosphonate Bis(1,2,2-trimethylpropyl) methylphosphonic acid	$C_{13}H_{29}O_3P$	7040-58-6	Impurity
Methyl pinacolyl methylphosphonate	NA	NA	Impurity
Methyl methylphosphonofluoridate	NA	NA	Impurity
Methyl methacrylate	$C_5H_8O_2$	80-62-6	Thickener

NA, not available. Data from Rosenblatt et al. (*13*), MacNaughton and Brewer (*27*), Kingery and Allen (*28*), Sanches et al. (*34*), and Johnsen and Blanch (*43*).

Cyanogen Chloride (CK)

CK (ClCN), a halogenated cyanide, is a colorless, highly volatile liquid that is highly irritating to the eyes and mucous membranes.

Table 24. Effects of acute exposure to pinacolyl methylphosphonofluoridate (soman; GD) degradation products, thickener, and contaminants.

Degradation product (formula; CAS no.)	LD_{50} or LC_{50}	LD_{LO} or LC_{LO}	Other effects
Methylphosphonic acid (MPA) ($C_3H_5PO_3$; 993-13-5)	Rat: oral, 5,000 mg/kg (*273*) Mouse: oral, > 5,000 mg/kg (*273*)		Human: skin and eye irritant (*274*)
Diisopropyl methylphosphonate (DIMP) ($C_7H_{17}PO_3$; 1445-75-6)	Rat: oral, 826 mg/kg (*350*) Mouse: oral, 1,041 mg/kg (*350*) Mink: oral, 503 mg/kg (*334*) Duck: oral, 1,490 mg/kg (*334*) Cattle: oral, ~ 750 mg/kg (*351*)		Draft ATSDR profile (*337*); examples follow: Rat: ataxia, decreased activity; prostration, 430 mg/kg LOAEL (*350*) Mouse: decreased activity; prostration, 430 mg/kg LOAEL (*350*) Mink: salivation, lethargy; immobilization, 300 mg/kg LOAEL (*334*)
Methylphosphonic difluoride (CH_3F_2OP; 676-99-3)	Mouse, dog: inhalation, 2,700 mg/m^3/30 min (*345*) Rat: inhalation, 8,100 mg/m^3/30 min (*345*) Monkey: inhalation, 3,000 mg/m^3/30 min (*345*) Guinea pig: inhalation, < 1,600 µg/L/1 hr (mg/m^3) (*352*)		Rat, mouse, dog, monkey: eye irritation (*345*) Rat, dog, monkey: corneal opacity, haze (*345*) Mouse: muscle weakness, ataxia (*345*) Dog, monkey: miosis (*345*) Rat, mouse, guinea pig: respiratory distress (*345,352*) Dog: pulmonary edema, congestion (*345*)
Methyl methacrylate ($C_5H_8O_2$; 80-62-6)	Rat: oral, 7,872 mg/kg (*378*) Mouse: oral, 3,625 mg/kg (*380*) Dog: oral, 4,725 mg/kg (*379*) Rabbit: oral, 8,700 mg/kg (*380*) Guinea pig: oral, 5,954 mg/kg (*379*) Rat: inhalation, 78,000 mg/m^3/4 hr (*381*) Mouse: inhalation, 18,500 mg/m^3/2 hr (*381*) Rabbit: skin, > 5 g/kg (*382*)	Dog: inhalation, 41,200 mg/m^3/3 hr (*379*) Rabbit: inhalation, 17,500 mg/m^3/4 hr (*378*) Guinea pig: inhalation, 19,000 mg/m^3/4 hr (*378*)	Rabbit: skin, irritation, 10 g/kg (*378*) Rabbit: eye, 150 mg (*379*)

Abbreviations: LC_{50}, medial lethal concentration; LC_{LO}, lowest lethal concentration; LD_{50}, median lethal dose; LD_{LO}, lowest lethal dose; LOAEL, lowest-observed-adverse-effect level.

Because of its volatility, it is considered a nonpersistent agent (*11*). CK and cyanide became the Allies' standard nonpersistent lethal agents early in World War II (*99*). This agent is not part of the U.S. CW stockpile but was used as training material at several sites in the United States; the continued presence of CK at these sites has not been verified (*230,231*). Without the addition of a stabilizer, CK may undergo polymerization to cyanuric chloride, which is corrosive and may explode (*15*). Chemical and physical properties of CK are listed in Table 1.

Formation of degradation products. At ambient temperature (25°C), CK is an extremely volatile liquid with a vapor pressure of 1,000 mmHg (*11*). No data were located on its fate in the atmosphere.

Because of its extreme volatility and relatively rapid rate of hydrolysis in water, CK is not expected to persist in surface waters. Hydrolysis half-lives range from 1 min at 45°C to 10 hr at 5°C (*398*). Kononen (*399*) calculated a hydrolytic half-life of 5.25 hr at 20°C and a pH of 8.64. The hydrolysis rate constant of CK at pH 7 is approximately 6.45×10^{-5}/mol/min (*9*). According to the American Public Health Association (*400*), CK may persist for 24 hr at a pH of 9.0 if no excess chlorine is present. CK undergoes considerable hydrolysis in the alkaline pH range to form cyanic acid (HOCN) and hydrochloric acid; the two reaction products are then converted to carbon dioxide (CO_2) and ammonium chloride (NH_4Cl). The same products form at a slower rate at acidic and neutral pH values (*9,401*):

$$ClCN + OH^- \rightarrow HOCN + Cl^-$$
$$ClCN + H^+ \rightarrow HOCN + H^+ + Cl^-$$
$$ClCN + H_2O \rightarrow HOCN + H^+ + Cl^-$$

CK from sources other than chemical agents may be present in natural waters. CK is formed by chlorine acting on dissolved or suspended organic matter including humic acids in the presence of ammonia or amines (*402*). CK is also formed by chlorine acting on cyanide ion or hydrocyanic acid in dilute aqueous solution (*9*). Disinfection of drinking water by chlorination results in the formation of chlorinated by-products including CK (*403–405*).

No data were located on the fate of CK in soil; however, its fate in soil would probably be similar to that in water, i.e., volatilization and hydrolysis.

Decontamination. No specific information was located on decontamination. CK is extremely volatile and undergoes rapid hydrolysis, which is accelerated if solutions are heated.

Acute and chronic mammalian toxicity. CK is highly toxic as a gas or liquid; it is converted in the body to hydrocyanic acid (HCN) and then detoxified to thiocyanate (*401*). The toxic effects of CK closely parallel those of cyanide (CN^-), producing respiratory failure by several means and blocking cellular energy metabolism (*167,240,401*).

Cyanic acid, the primary hydrolysis product of CK, is toxic by the oral, ip, and intramuscular routes. Its lethality is evidenced by data for its sodium salt, CNO•Na, which includes a mouse oral LD_{LO} value of 4 mg/kg (*240*) and a rat oral LD_{50} value of 1,500 mg/kg (*406*). Intramuscularly, the rat LD_{50} value is 310 mg/kg (*240*), whereas the mouse ip LD_{50} value is similar, 260 mg/kg (*406*), again for the sodium salt of cyanic acid. No toxicity test data were found for cyanic acid. Cyanic acid is a vesicant and strong lacrimator, causing severe irritation to the eyes, skin, mucous membranes, and respiratory tract (*14*). According to Lewis (*240*), human ingestion can result in weight loss and eye effects including visual field changes. No occupational or environmental regulations or guidelines were found for cyanic acid.

Ecotoxicology. CK is extremely toxic to aquatic organisms, with 48-hr and 96-hr LC_{50} values for aquatic invertebrates and fish of < 150 µg/L (*399,407*). Toxicity may be attributable, at least partially, to the free cyanide (CN^-) in solution. The 96-hr LC_{50} values of free cyanide for fathead minnows at pH values of 8.29 and 8.67 were 120 and 110 µg/L, respectively (*408*). No information was located on the toxicity of cyanic acid.

Conclusions

We examined sources of information such as field and laboratory studies as well as reports on analyses of storage containers at burial or unitary stockpile sites in this review to determine the presence of degradation products, contaminants, and impurities of CW agents. For completeness, we included all identified organic compounds unless they were common and already well understood toxicologically. Few or no data on degradation pathways, mammalian toxicity, or ecotoxicity are available for many of the rather obscure CW degradation products. Of those substances for which both toxicity and environmental fate data are available, it is clear that very few of the degradation products are both environmentally persistent and highly toxic. Compared with most hazardous environmental contaminants, the CW agents show a unique propensity to hydrolyze. The nerve agents are so hydrolytically labile that they are predicted to persist in the environment for no more than a few days. Such susceptibility by the parent agents and their more toxic intermediate degradation products minimizes the likelihood of groundwater contamination, given the nature of the leaching and percolation processes involved in movement through soil to groundwater. Of those degradation products known to exhibit significant environmental persistence, most are minimally to moderately toxic.

The CW degradation products of primary interest include TDG for HD; Lewisite oxide for Lewisite; and EA 2192, EMPA,

Table 25. Carcinogenicity, genotoxicity, reproductive toxicity, and systemic effects of chronic exposure to pinacolyl methylphosphonofluoridate (soman; GD) degradation products, thickener, and impurities.

Degradation product (formula; CAS no.)	Carcinogenicity	Genetic effects	Reproductive effects	Systemic effects
Methyl methacrylate, ($C_5H_8O_2$; 80-62-6)	Mouse: rat, inhalation, negative (*384*) Rat: oral, negative (*388*)	Mutagenicity: positive, *Salmonella* (*385*) Mutagenicity: Ames, negative (*222*) Mutagenicity: positive, mouse lymphoma cells (*391*) Micronucleus test: equivocal, mouse lymphocyte (*391*) Mutation: mouse lymphoma cells, positive, with activation (*394*) Cytogenetic effects: positive, several end points (*384,391,394*) SCE: positive; hamster ovary (*384*) Mouse: negative, RDS test (*166*)	Rat: inhalation, fetotoxicity, growth retardation; embryolethality (*386*) Rat: inhalation, postimplantation mortality (*389*)	Human: contact dermatitis (*387*) Rat: inhalation, serum composition, cholesterol, bilirubin, transaminases, nutrition/metabolic effects (*390*) Rat: inhalation, focal lung fibrosis, olfactory sensory epithelium degeneration, nasal cavity inflammation (*392*) Rat: oral, somnolence, neurostructural changes, lipid effects (*393*) Mouse: inhalation, zonal hepatocellular necrosis, olfactory sensory epithelium degeneration, nasal cavity inflammation, epithelial hyperplasia (*384*)

Abbreviations: RDS, replicative DNA synthesis; SCE, sister chromatid exchange.

and MPA for VX. MPA is also a product of both GB and GD degradation. The GB contaminant, DIMP, is also of interest because of its environmental persistence, whereas the closely related IMPA is a hydrolysis product of GB that slowly hydrolyzes further to MPA. Of these degradation products, only Lewisite oxide and EA 2192 possess high mammalian toxicity.

The information on these and other toxic or persistent degradation products of possible concern is summarized in the following discission and in Table 26, grouped by parent CW agent. We do not consider the contaminants/degradation products present at < 0.1% in ton containers of HD or VX to be of environmental concern because amounts are so small. Furthermore, these trace compounds have not been identified following pilot studies of agent neutralization, indicating their probable destruction.

Sulfur mustard (HD). For HD dispersed in the environment, TDG and 1,4-oxathiane are the primary hydrolysis end products. For bulk mustard in the environment, the sulfonium ion aggregates such as mustard–TDG and hemimustard–TDG are of some importance. The most persistent degradation product of HD, and therefore the substance of primary interest, is TDG. Several additional persistent products are also discussed.

TDG is the main hydrolysis product of HD prior to mineralization; it does not undergo further hydrolysis but is susceptible to microbial degradation, the latter being the basis for the final phase of the disposal technology for HD stored in bulk. TDG is of low acute and chronic toxicity to mammals (Tables 4 and 5) and aquatic organisms. Additionally, it is not a product unique to HD degradation, as it is used as a solvent in printing and in antifreeze solutions.

Sulfonium ion aggregates (mustard and hemimustard–TDG aggregates) may be persistent in the environment and retain their vesicant properties, but according to available information, they are generally of low oral toxicity to mammalian species (Table 4). However, the H–TDG aggregate has considerable toxicity when applied dermally. The HD–2TDG aggregate was almost nontoxic to aquatic organisms.

Mustard sulfoxide, mustard sulfone, and divinyl sulfone are oxidation products and so may be formed in the environment to a lesser degree than hydrolysis products. They are relevant when considering decontamination. The sulfoxide is extremely stable to hydrolysis but is considered only slightly toxic (Table 4). Mustard sulfone retains vesicant properties and is approximately 0.1 times as toxic as distilled mustard by iv and sc routes and half as toxic by inhalation. Divinyl

Table 26. Summary of known persistent or toxic chemical warfare agent degradation products.

Chemical warfare agent	Degradation process	Degradation product	Persistence/ parameters[a]	Relevant routes of exposure	Toxicity[b]
Sulfur mustard	Hydrolysis	Thiodiglycol	Moderate/nonvolatile, miscible with water, resistant to hydrolysis, biodegradable	Oral	Low[c]: rat oral LD_{50}, 6,610 mg/kg (*63*)
Lewisite	Hydrolysis, dehydration	Lewisite oxide[d]	High/water insoluble, potential oxidation (soil)	Dermal	Unknown (dermal irritant, vesicant)[e]
O-ethyl-*S*-[2-diisopropylaminoethyl] methylphophonothioate (VX)	Hydrolysis	EA 2192	Moderate/low volatility, high water solubility, resistant to hydrolysis	Oral	High[e]: rat oral LD_{50}: 0.63 mg/kg (*255*)
		EMPA	Moderate/low volatility, water soluble, resistant to hydrolysis, biodegradable[g]	Oral	No data[f]
	Formed from EMPA	MPA	High/low volatility, resistant to photolysis, high water solubility, resistant to hydrolysis, mobile in soils, biodegradation resistant	Oral	Low[c]: rat oral LD_{50}: 5,000 mg/kg (*273*)
Isopropyl methylphosphonofluoridate (GB)	Hydrolysis	IMPA	High/low vapor pressure, water soluble, resistant to hydrolysis, biodegradation resistant	Oral	Low[c]: rat oral LD_{50}: 6,070 mg/kg (*348*)
		MPA	High/low volatility, resistant to photolysis, high water solubility, resistant to hydrolysis, mobile in soils, biodegradation resistant	Oral	Low[c]: rat oral LD_{50}: 5,000 mg/kg (*273*)
	Impurity	DIMP	High/low volatility, water soluble, resistant to hydrolysis, slow biodegradation	Oral	Low[c]: rat oral LD_{50}: 826 mg/kg (*350*)
Ethyl *N,N*-dimethylphosphoroamidocyanidate (GD)	Hydrolysis	MPA	High/low volatility, resistant to photolysis, high water solubility, resistant to hydrolysis, mobile in soils, biodegradation resistant	Oral	Low[c]: rat oral LD_{50}: 5,000 mg/kg (*273*)

Abbreviations: DIMP, diisopropyl methylphosphonate; EA 2192, *S*-(2-diisopropylaminoethyl) methylphosphonothioic acid; EMPA, ethyl methylphosphonic acid; IMPA, isopropyl methylphosphonic acid; LD_{50}, median lethal dose; MPA, methyl phosphonic acid.
[a]Persistence depends on environmental conditions. In general, moderate persistence indicates weeks to months and high persistence indicates months to years. [b]Toxicity by relevant route of exposure. [c]Does not retain the toxic properties of the parent chemical warfare agent. [d]Under continually moist conditions, the hydrolysis product 2-chlorovinyl arsonous acid, a probable vesicant, may be present. [e]Retains the toxic mechanism of action of the parent chemical warfare agent. [f]Structural similarity to that of IMPA may indicate a similar low toxicity. [g]Disappearance from soil may be due to a combination of hydrolysis and biodegradation.

sulfone is a vesicant and is highly toxic by the oral route. Some sources characterized mustard sulfoxide and mustard sulfone as highly toxic but lacked data for environmentally relevant routes of exposure. These compounds are moderately water soluble, which may limit their environmental persistence. Literature searches located no environmental toxicity data for these compounds.

1,4-Dithiane and 1,4-oxathiane are often referred to as thermal degradation products but are present as impurities in ton containers of mustard; 1,4-oxathiane is also a hydrolytic degradation product. Both products are groundwater contaminants in the Rocky Mountain Arsenal area, indicating environmental persistence. Both are of low acute toxicity to mammalian species (Table 4). Additionally, subchronic administration of 1,4-dithiane to rats at doses up to 420 mg/kg/day produced no overt toxicity (Table 5). No environmental toxicity data were located.

Other impurities of HD include 1,2-bis(2-chloroethylthio)ethane and 1,8-dichloro-3-oxa-6-thiaoctane. Impurities are usually present in very small amounts. Human and laboratory animal data indicated moderate-to-high toxicity for 1,2-bis(2-chloroethylthio)ethane by the inhalation route (Table 4). There are probably other impurities such as isomers of HD that are highly vesicant, but these would be present in very small amounts (< 1%).

Nitrogen mustards. The nitrogen mustards were manufactured in limited quantities; they were never stocked as a significant part of the U.S. CW inventory and thus are of limited environmental concern. The nitrogen mustards are fairly persistent: HN1 and HN2 are moderately persistent and HN3 is quite persistent, although the latter slowly degrades to triethanolamine. The main degradation process is expected to be hydrolysis. Inhalation exposures are not a concern because all three agents have low vapor pressures. Although the intermediate hydrolysis products are of moderate-to-high toxicity and irritancy to mammals (Table 7), the later hydrolysis products such as diethanolamine and triethanolamine are generally of low acute toxicity to mammals and aquatic organisms.

Lewisite. Lewisite was also produced in limited quantities. It is stored in bulk at only one site, with smaller amounts possibly present at several other sites. Lewisite gives rise to two hydrolysis products, one of which (Lewisite oxide) is a highly toxic vesicant (Table 11). No toxicity data are available for the other Lewisite hydrolysis product 2-chlorovinyl arsonous acid, but this compound retains most of the Lewisite structure. In solution, Lewisite yields 100% 2-chlorovinyl arsonous acid, but the insoluble Lewisite oxide is formed after drying. In soil, Lewisite oxide can be converted to 2-chlorovinyl arsonic acid, which is moderately acutely toxic to rats by the oral route. These organic arsenicals are not likely to exhibit carcinogenicity themselves, but in the course of complete mineralization they form various inorganic arsenic compounds that are potentially carcinogenic and are of possible concern with regard to worker safety. The U.S. EPA has set oral and inhalation slope factors for inorganic arsenic. However, the small quantity of Lewisite produced makes its degradation products of limited environmental concern.

VX. Agent VX forms a variety of degradation products, one of which retains significant toxicity, whereas several others, including MPA, have low-to-negligible toxicity. The most persistent products in weathered soil samples are EA 4196 and MPA. The most toxic is EA 2192.

Several literature sources indicated that EA 4196 is environmentally stable and tightly bound to soil, but gave no specific characterization data (*254,259*). Environmental monitoring data were not located, but it would be of interest to know whether this substance has been identified in soil or water at contaminated sites. Mammalian and ecotoxicity data were also unavailable.

The intermediate VX hydrolysis product EA 2192 may be stable in water under certain pH conditions but is degraded as rapidly as VX in soil. According to limited data, it is a highly toxic anticholinesterase agent depending on the route of exposure (Table 14). EA 2192 is only slightly less toxic than VX by the iv route but is 0.1–0.2 times as toxic as VX orally. It does not penetrate the skin when applied in a water or alcohol solution, and its volatility is thought to be too low to pose an inhalation hazard. No ecotoxicity data were located for this compound. It is unclear whether EA 2192 is sufficiently persistent to be of concern.

MPA is an ultimate hydrolysis product for VX, GB, and GD. It is environmentally persistent and was detected for up to 10 years following contamination of the dry soil at Dugway Proving Ground. MPA has low toxicity to both mammals and aquatic organisms.

EMPA may be persistent in the environment under some conditions, as hydrolysis to MPA has not been shown in a laboratory setting. However, hydrolysis to MPA in soil does occur. Experimental toxicity data are not available for EMPA. Because the structure of EMPA is similar to that of IMPA, which exhibits low mammalian toxicity, EMPA is predicted to exhibit low mammalian toxicity.

GA. This agent was produced in very limited quantities and is presently stored only at Tooele Army Depot. The production process results in numerous contaminants and impurities. The initial hydrolysis products ethylphosphoryl cyanidate and ethyl *N,N*-dimethylamido phosphoric acid probably retain some toxic properties. However, searches located no data on unique degradation products or GA contaminants and impurities. Toxicity data were located for dimethylamine and triethyl phosphate (Tables 18 and 19); however, these compounds are not unique to GA degradation. The small quantity of GA produced, distributed, and stored makes this compound of limited environmental concern.

GB. Agent GB is essentially nonpersistent, as it is volatile, water soluble, and subject to both acidic and basic hydrolysis. The degradation products are considered nontoxic. The primary hydrolysis product IMPA, although environmentally persistent, is of low acute oral toxicity in rats and mice (> 5,000 mg/kg) (Table 21). IMPA slowly hydrolyzes to MPA, which is persistent in the environment but is essentially nontoxic to mammalian and aquatic organisms. The U.S. EPA has derived an RfD of 0.1 mg/kg/day for IMPA.

An impurity of GB, DIMP, has raised concern because it is environmentally persistent and has been found in groundwater at Rocky Mountain Arsenal. Mammals rapidly metabolize DIMP to IMPA; DIMP has demonstrated low acute (Table 21) and negligible chronic (Table 22) toxicity in several mammalian species. It is also of low toxicity to mammalian wildlife and aquatic organisms. Controversy over drinking water standards for DIMP and thus its cleanup criteria has arisen because of deaths in a reproductive toxicity screening study with mink (*334*). The deaths were probably due to nursing or stress syndrome, a syndrome thought to be unique to mink. These deaths appear to have been misattributed to DIMP toxicity by some, but the state of Colorado has based its groundwater and surface water standards on the LOAEL from this study. The U.S. EPA based its less conservative drinking water criteria instead on an oral subchronic DIMP study in dogs.

Methylphosphonic difluoride, a precursor and contaminant of GB that has irritant and anticholinesterase properties (Table 21), rapidly hydrolyzes in water to MPA and hydrogen fluoride.

GD. Agent GD is not part of the U.S. chemical inventory and so may be of limited environmental concern. However, experimental quantities exist in the United States, and GD was the primary G agent manufactured by the former Soviet Union. No information was located on the primary hydrolysis product pinacolyl methylphosphonic acid, but its structure is similar to that of IMPA,

which exhibits low mammalian toxicity, and it also slowly hydrolyzes to MPA.

Cyanogen chloride. CK hydrolyzes rapidly under alkaline conditions to HCl and cyanic acid, which is highly toxic by all routes of exposure. Cyanic acid and HCl slowly form CO_2 and ammonium chloride in an aqueous environment.

Summary

We reviewed the degradation of three types of vesicant CW agents, the sulfur mustards, nitrogen mustards, and Lewisite. Because of its persistence, the major hazard in HD-contaminated sites is probably HD itself. Sulfonium ion aggregates formed during hydrolysis may be persistent and may retain vesicant properties. Decontamination gives rise to two toxic oxidative dechlorination products, mustard sulfone and divinyl sulfone. The final hydrolysis product, TDG, may be persistent but exhibits low toxicity. Similarly, HN agents themselves are both highly toxic vesicant agents and are relatively persistent, and their initial hydrolysis products are also of high toxicity. Diethanolamine and triethanolamine are only slightly toxic. Under varying moisture, Lewisite gives rise to two toxic hydrolysis products, 2-chlorovinyl arsonous acid and Lewisite oxide. Almost no mammalian toxicity data are available for these two hydrolysis products or for the Lewisite oxidation product 2-chlorovinyl arsonic acid.

The nerve agents include the V agent VX as well as three G agents. VX gives rise to two hydrolysis products of possible concern: EA 4196, which is persistent, and EA 2192, which is highly toxic and is possibly persistent under certain limited conditions. The alkyl methylphosphonic acids, hydrolysis products of the G agents, although environmentally persistent, do not appear to present significant hazards from the standpoint of toxicity.

The blood agent CK is extremely volatile and undergoes rapid hydrolysis. Thus, environmental persistence should not be a concern. The primary degradation products, cyanic acid and HCl, should be mineralized under environmental conditions. Like GA, GD, and Lewisite, however, CK is not a major part of the United States CW inventory.

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