

The designation of these agents as “skin damaging” gives an incomplete picture of their effects. The several mustards, lewisite, and phosgene oxime have quite different chemistries and mechanisms of action (some of which are poorly understood), but all are capable of eye damage at low levels, pulmonary injury at any level, and notable systemic effects at higher doses. Systemic illness can result from skin absorption alone. It is a maxim in chemical casualty care that, when eye effects occur, pulmonary injury should also be suspected (Rebentisch and Dinkloh, 1980).

Within the context of the Gulf War, typical military level-exposures to these agents would have been readily recognized, particularly when there was so much concern about chemical attacks. At low levels of exposure there may have been some opportunities for very mild cases to go unrecognized in a setting in which eye irritation from sand and other factors was common, as were respiratory symptoms (Korenyi-Both and Juncer, 1997). It seems unlikely that typical vesication (blisters) would have escaped notice, but lesser levels of exposure can resemble sunburn. OSAGWI has located hospital records that can be examined for admissions for blistering. If unit medical records documenting sick-call workloads can be located for the periods before and after hostilities began, it may be possible to compare them to look for a change in the pattern of illness.¹ Hospital experience was also extensive with outpatients, as West (1993) described for the 13th Evacuation Hospital, suggesting other retrievable records.

The agents under consideration vary greatly in the timing of the onset of clinical signs and symptoms: immediately for phosgene oxime, promptly for lewisite (seconds to minutes), and delayed (hours) for mustards.

¹Hines (1993) reports sick call for the First Cavalry Division for November–February, so some records may still exist.

These agents play a variety of military roles, especially to create barriers or deny terrain and facilities (mustards and lewisite), by virtue of their persistence and the ability to create vapor and contact hazards. All can be used in conjunction with other, more toxic agents to enhance their effects, and all are dangerous as vapors, aerosols, or droplets. While these agents are dangerous when ingested, it does not appear that there was much opportunity for food and water contamination during the Gulf War. There are indications that it is possible to disseminate mustards adsorbed on small particles (Dunn, 1986).

Research information is uneven, with little information available on phosgene oxime and only small amounts on the others from the 1960s and 1970s. Modern research techniques have only recently been applied, as a result of concerns about occupational and civilian population exposure risks from demilitarization efforts and recognition of continued use and threats arising from these agents.

LEWISITE

History and Background Information

Lewisite (also known as Agent L), is no longer considered a state-of-the-art chemical warfare agent (Franke, 1967; SIPRI, 1971; SIPRI, 1973) but remains in many countries' stockpiles. Lewisite is relatively simple and inexpensive to produce, making it attractive to less advanced nations beginning chemical warfare programs (Franke, 1967).

Lewisite acts promptly on exposure, persists with moderate potency, and is easily mixed with other chemical agents to augment toxic effects. For example, HL (a mustard-lewisite mixture) is less likely to freeze when dropped from high altitudes. Lewisite can be most effective when mixed with nerve agents. Once absorbed, lewisite induces vomiting, precluding the use of protective masks and making personnel vulnerable to other, more toxic chemicals. Lewisite is a significant threat to unprotected personnel for that reason and also because it causes prompt incapacitation from eye injuries and respiratory irritation, coupled with long-term incapacitation from skin burns, pulmonary injury, and systemic illness (Sidell, Takafuji, and Franz, 1997, pp. 218–220).

Both the United States and Germany synthesized and characterized lewisite during World War I but did not use it during that conflict. The Germans chose not to develop it, apparently because they regarded its prompt irritating effects as a disadvantage, especially contrasted to the delayed and initially unnoticed effects of mustards (Wachtel, 1941). Large munitions expenditures were required to achieve effective concentrations in the field (Pechura and Rall, 1993, pp. 25–29). The United States, Germany, Russia, and Japan built considerable

stocks of lewisite during World War II (Franke, 1967; SIPRI, 1971). The Japanese used lewisite against Chinese troops repeatedly before and during World War II, in some cases to impede withdrawing forces (SIPRI, 1971), although the effects are not documented.

Although the use of lewisite was suspected at times during the Iran-Iraq War, it was never proved present in the munitions studied (UN, 1984; Dunn, 1986; Defense Intelligence Agency, 1997) and no elevated levels of arsenic were found in the blood and tissues of Iranian casualties treated in Europe (Heyndrickx, 1984, pp. 90–101).

There is some human exposure experience from accidental exposure to lewisite (Cogan, 1943), human experimentation, and occupational exposures of production workers (although governmental follow-up of these exposures has been criticized for lack of persistence) (Pechura and Rall, 1993). The levels of exposure that resulted from accidents in occupational workers are not known. The accident Cogan (1943) reported involved a group of officers observing a test, who thought they had encountered a riot control agent.

Weaponization

Lewisite is easy to manufacture, and storage stability problems can be overcome. It can be dispersed by aerial spraying, shells, or bombs. Lewisite persists for six to eight hours on the ground in sunny weather. Thickened forms to enhance persistence have been tested. Its decomposition products are toxic, making decontamination difficult. Munitions containing lewisite may contain toxic stabilizers. Lewisite is effective as vapor, aerosol, or liquid.²

Detection

There are reports, although they are variable and unreliable, of a characteristic (geraniumlike) odor for lewisite in the range of 0.8 mg/m³ to more commonly cited 14 to 23 mg/m³ median detection (OSRD, 1946; Pechura and Rall, 1993, p. 53). Detecting lewisite has not been a high military priority. U.S. forces have detectors for lewisite—paper and kits (M7 and M9A)—and the Fox reconnaissance vehicle is able to detect lewisite with its mass spectrometer system. Other forensic techniques for soil and material analysis exist (e.g., gas chromatography). In biological tissues, increased arsenic levels are a surrogate for lewisite (Haddad and Winchester, 1983).

²Goldman and Dacre (1989) provided a comprehensive review, and Pechura and Rall (1993) provided an extensive bibliography as an annex.

Chemical and Physical Characteristics

Table 3.1, compiled from Field Manual 3-9 (U.S. Army, 1990), shows the chemical structure of lewisite and some of its important properties. This agent is somewhat volatile, more than mustard but less than water.

Toxicology and Toxicokinetics

Lewisite is a local and pulmonary irritant, a vesicant, and a systemic poison. When ingested with food, it produces severe gastrointestinal irritation. The eyes, respiratory tract, and skin are the most likely sites of exposure when lewisite is used as a chemical warfare agent. The agent is lipophilic and readily penetrates intact skin (Wachtel, 1941; Vedder, 1925; North Atlantic Treaty Organization [NATO], 1973). The approximate lethal dose (LD_{50} , dose expected to kill 50 percent of humans) is 35 to 40 mg/kg, an amount present in 2 ml of liquid agent. However, 1 g on the skin causes severe internal organ injury (NATO, 1973). Lewisite toxicity resembles other trivalent arsenicals that produce peripheral and central neurotoxicity, hepatotoxicity, and epithelial damage.³ Death may result from fluid loss and hypovolemia secondary to capillary leakage—the so-called “lewisite shock” (Snider et al., 1990; Watson and Griffin, 1992; Sidell, Takafuji, and Franz, 1997, pp. 218–220). The effects noted above are from higher dose exposures.

Early studies of arsenic compounds showed that the toxicity was associated with altered cellular metabolism. The cellular poisoning effects are attributed to the inhibition of cellular enzyme systems (Watson and Griffin, 1992; Pechura and Rall, 1993), especially as a result of arsenic complexing with sulfhydryl groups of proteins and enzymes. This agent affects many sulfur-containing enzymes, including amylase; lipase; cholinesterase; some adenosine triphosphate (ATP) enzymes; creatine phosphokinase; and, of central importance (Snider et al., 1990), the pyruvate oxidase system.

According to the *Textbook of Military Medicine* (Sidell, Takafuji, and Franz, 1997, pp. 218–220), there are two types of mechanisms for these effects:

1. reactions with glutathione leading to loss of protein thiol status, loss of calcium ion homeostasis, oxidative stress, lipid peroxidation, membrane damage, and cell death
2. reactions with sulfhydryl groups on enzymes leading to inhibition of pyruvate dehydrogenase complex, inhibition of glycolysis, loss of ATP, and cell death.

³Most human experience with trivalent arsenicals is from oral toxicity (Haddad and Winchester, 1983).

Table 3.1
Lewisite: Attributes and Responses

Agent	Lewisite Agent L Dichloro(2-chlorovinyl)arsine
Agent type	Rapid-acting blister casualty agent
Chemical structure	$\begin{array}{c} \text{H} \quad \text{H} \\ \quad \\ \text{Cl} - \text{C} = \text{C} - \text{As} \begin{array}{l} / \text{Cl} \\ \backslash \text{Cl} \end{array} \end{array}$
Physical/chemical properties	
Vapor density	7.1 (compared to air)
Freezing point	18 to 0.1°C (purity- and isomer-dependent)
Boiling point	190°C
Vapor pressure	0.394 mm Hg at 20°C
Volatility	4,480 mg/m ³ at 20°C
Decomposition at	>100°C
Hydrolysis rates ^a	Degrades under humid conditions Vapor—rapid Dissolved—rapid
Hydrolysis products	HCl and chlorovinyl arsenous oxide; alkaline hydrolysis destroys blister properties
Toxicity	
Median incapacitating dosage	
Respiratory	Not listed
Skin vapor	>1,500 mg-min/m ³
Eye vapor	<300 mg-min/m ³
Median lethal dosage	
Respiratory	1,200–1,500 mg-min/m ³
Skin liquid	Not listed
Skin vapor	100,000 mg-min/m ³
Symptoms	Immediate stinging to skin, blistering of skin (after 13 hours), respiratory inflammation—plus systemic poisoning
Protection required	Protective impermeable clothing and masks and gloves at all times
Decontamination	Personnel—Washing soda, skin decontamination pads, alkaline soap or detergent and water
First aid	Decontaminate, provide support, British antilewisite (BAL)
Detection method	M256 kit for high concentrations on surfaces or in air; bubbler method for low concentrations

SOURCES: U.S. Army (1990); AD Little (1986, Ch. 2).

^aLow solubility in water limits hydrolysis.

In vitro studies show that lewisite at 0.3 µg/l stops cell proliferation and inhibits DNA synthesis (Henriksson et al., 1996). Laminin, an adhesion molecule in the basement membrane of the skin, is rich in sulfhydryl groupings, so it is suspected that inhibition of this molecule is the mechanism by which lewisite causes blisters (King et al., 1994). In a rabbit whose skin is exposed to lewisite liquid, absorption of arsenic is very rapid, with the highest levels appearing in the liver, lungs, kidney, spleen, and intestines (Cherkes, 1965). In a more recent rabbit study (Snider et al., 1990), lewisite was widely distributed in the body, with high concentrations (e.g., seven times the blood level) found in liver, lung, and kidneys. Tissue levels actually rose over the course of four days, even as blood levels fell. In the Cherkes (1965) study, arsenic appeared in the urine after a few hours. The kidneys, and to a lesser extent the bile, were the main excretion routes. Although the mechanism of vomiting is not known, arsenic has been shown to bind to, and inactivate, muscarinic receptors (Fonseca et al., 1991).

Exposure-Effect Relationships

Table 3.2 shows incapacitating levels of lewisite. Data from various sources do not agree on irritating and incapacitating effects, and no available information resolves the differences. The tolerance threshold for the irritant effects of lewisite is approximately 0.8 mg/m³ (Wachtel, 1941). Definite eye and respiratory irritation occurs within 1 minute at concentrations of 10 to 30 mg/m³. Vapor concentrations sufficient to cause blisters are lethal if inhaled. Unmasked personnel exposed to lewisite vapor would probably not show skin burns because eye and respiratory signs would overcome personnel first. A small amount of liquid on the skin or eyes is hazardous; 0.1 µl in the eye blinded rabbits (AD Little, 1986, Ch. 2; Aponte et al., 1975).

No references discussing interactions with medications or environmental chemicals were located. There are no reports of individuals' developing hypersensitivity to lewisite, as has been seen with mustards. Although arsenic can produce a polyneuropathy, no reports emerged of such peripheral neuropathy in humans or animals following acute lewisite exposure. Arsenic polyneuropathy is more often seen in a setting of chronic exposure (Harrison, 1997).

There is little information regarding chronic and long-term exposures (Watson and Griffin, 1992; Lohs, 1975; Pechura and Rall, 1993). Although there is some information from Japanese munitions workers, occupational exposures from manufacturing have not been well-studied. Judging such exposures is difficult because these workers worked with other arsenicals and mustards, and actual exposure levels were unknown. A 1978 study of Japanese workers (Inada et al., 1978) demonstrated an increased risk of intraepithelial Bowen's squamous cell carcinoma (Pechura and Rall, 1993, p. 99).

Table 3.2
Incapacitating Levels of Lewisite

Exposure	Species	Dose	Comments	Sources	
Eye	Human	2.0 mg/m ³	Irritation threshold	Cherkes (1965), Aleksandrov (1969)	
	Human	10 to 30 mg/m ³	Definite irritation in 1 min.	Cherkes (1965)	
	Human	1 to 5 mg/m ³	Intense irritation	Stade (1964)	
	Rabbit	0.1 µl	Liquid; permanent blindness	Aponte et al. (1975)	
	Human	10 mg/m ³	Vapor; inflammation and swelling of eye and lids	Franke (1967)	
			0.8 mg/m ³	Vapor; limit of tolerance	
	Human	1,500 mg-min/m ³	CT, permanent eye damage		
	Human	<300 mg-min/m ³	Concentration required for incapacitation due to eye irritation		
Skin ^a	Human	0.01 mg/cm ²	Erythema; liquid	Cherkes (1965),	
		0.05 to 0.1 mg/cm ²	Erythema; liquid	Franke (1967)	
		0.15–0.2 mg/cm ²	Blisters; liquid	Franke (1967)	
		10,000 mg/m ³	Blisters; vapor concentration; 15 min	Franke (1967)	
		2,000 mg/m ³	Erythema; vapor; 1 hour	Aleksandrov (1969)	
		2,800 mg/m ³	Blisters; vapor; 1 hour	Aleksandrov (1969)	
		3,340 mg/m ³	Blisters; vapor concentration	Wachtel (1941)	
Inhalation	Human	10 to 30 mg/m ³	Vapor—injury to the upper respiratory tract	Aleksandrov (1969)	
	Human	50 mg/m ³	Vapor—incapacitation for several weeks	Franke (1967)	

SOURCE: Various (AD Little, 1986, Ch. 2).

^aErythema/blistering.

Chronic cough and eye irritation can be expected from exposure to lewisite. It is uncertain whether chronic bronchitis or asthma results from lewisite exposure, although reactive airway disease after severe irritations is recognized.

Lohs (1975) warns of the neuropathic capabilities of arsenicals; however, none of the follow-up studies has mentioned neuropathy. There is no indication that chronically occupationally exposed persons develop chronic oral arsenic intoxication with anemia, hyperkeratosis, inflamed mucous membranes, and polyneuropathy (motor and sensory) (Harrison, 1997). Studies of long-term

exposure (13 weeks average) of rats to lewisite found no effects on body weight or reproduction with up to five 2-mg/kg doses by gavage per week (Sasser et al., 1996). There was gastric irritation. The no-observed-adverse-effect level was estimated to be between 0.5 and 1mg/kg.

In general, extrapolations from animal studies have served to set exposure standards and estimate human effects, particularly to understand severe intoxication. Low-dose studies have not been found. The Surgeon General's Working Group (Morbidity and Mortality Weekly Report [MMWR], 1988) established the following exposure standards: a time-weighted average level of 0.003 mg/m³ for 8 hours for workers and 72 hours for the general public (see DHHS, 1988)⁴.

Clinical and Pathological Findings

There are few published case reports of human lewisite poisoning. Soviet authors describe clinical findings that may have arisen from accidents but provide no details. Cogan (1943) reported an accidental vapor exposure of several officers who initially thought they had been exposed to "tear gas" and had sustained mild eye injuries. Volunteer studies give a picture of the course of skin injuries. Signs and symptoms of acute lewisite exposure include the rapid onset of irritation to the eyes and mucous membranes of the upper respiratory tract (lachrymation and rhinitis). In more serious cases of vapor intoxication, chest pain, nausea, vomiting, headache, weakness, convulsions, hypothermia, and hypotension occur (Sidell, Takafuji, and Franz, 1997; Karkchiev, 1973; AD Little, 1986, Ch. 2; U.S. Army, 1990; NATO, 1973). Other than serious eye injuries, most acute injuries seem to resolve well.

The pathology literature is largely limited to serious acute exposures (e.g., Vedder, 1925). Laboratory tests of the blood of persons exposed may show hemoconcentration; animal studies suggest elevated liver enzymes, including lactate dehydrogenase (LDH) (King et al., 1992; Sasser et al., 1996). Blood arsenic would be detected at toxic levels. The following subsections describe the effects on specific body sites.

Skin. Exposure of the skin to vapor causes immediate itching or stinging within one minute, followed by erythema over 10 to 30 minutes. Mild exposures resemble a sunburn, with pain decreasing over 24 to 48 hours, sometimes followed by desquamation. More intense exposures, including liquid contact, produce intense stinging and the formation of small vesicles over the next 24 hours, with later enlargement of the vesicles with accumulation of a nontoxic fluid. Gradually, a crust forms, and the lesion dries. The skin shows degenera-

⁴That is, the public is permitted one-ninth the worker exposure.

tive, necrotic changes with edema, hemorrhage, and inflammation. The scrotum, axillae, and neck seem most sensitive.

A deep bullous lesion occurs following heavy exposure, worsening over three to four days, with considerable pain. Such lesions take one to two weeks to resolve, a shorter period than with a similar mustard injury.⁵ Systemic illness is more likely to occur if such heavy exposures are to the liquid form, with later development of vomiting, pulmonary edema, or shock.

Eye. Immediate eye pain and blepharospasm result from lewisite exposure, followed by conjunctival and lid edema. Within one hour, the lids are closed, and photophobia and headache (perhaps from ciliary spasm) occur. After a few hours, the edema decreases, but corneal opacity and iritis may occur. Severe exposures can produce necrotic injuries of the iris with depigmentation, hypopion, and synechia development. In contrast, very low levels may only involve the conjunctivae. Unlike mustard exposure, there is no latent period.

The pathology of severe eye injuries is not relevant to this review. Mild eye exposures (Cogan, 1943) showed dilated pericorneal vessels, violaceous flush of the ciliary region, and later changes similar to dendritic keratitis in the cornea. A relapsing syndrome (apparent recovery followed by return of keratitis) like that of mustard injury has not been described for lewisite.

Respiratory. Mild respiratory exposures resemble upper respiratory infections, with sneezing, coughing, rhinitis, and mucous membrane erythema, possibly progressing to retrosternal pain, nausea, and malaise. More severe exposures cause lower respiratory effects, with continuous coughing, laryngitis, and aphonia. Crackles and rales may be heard over the lung fields, and mucous and sputum production are abundant. Tracheobronchitis develops more rapidly and is more severe than with mustards. Pneumonia and pulmonary edema may develop on the first day. German authors (see AD Little, 1986, Ch. 2) have described in occupational settings a chronic cough and bronchitis with abundant sputum production that was described as "sweet." There are descriptions of severe pulmonary lesions resulting from serious acute exposure in dogs (Vedder, 1925).

Nervous System. Despite reports of convulsions and coma with severe exposures, neurological findings are inconsistent. Neurologic complications after mild exposures have not been described. Some Soviet authors have reported edema and hemorrhage in the brain, but such findings have not been noted in U.S. studies. No reports of degeneration of peripheral nerves were found.

⁵Generally, lewisite injuries respond more favorably than mustard injuries (Wachtel, 1941, Vedder, 1925).

Cardiovascular. In severe intoxication, there may be bradycardia, dyspnea, hypotension, and hemoconcentration. These effects are mediated by vasodilation and increased capillary permeability, which can produce lewisite shock (Watson and Griffin, 1992). Soviet investigators describe patchy subendocardial hemorrhages as characteristic of lewisite toxicity in animals (AD Little, 1986, Ch. 2). Other studies noted dilation of the right side of the heart in severe animal poisoning.

Other Systems. Human ingestion experience is not documented (NAS, 1985), but would be expected to produce severe abdominal pain and bloody diarrhea. Nausea and vomiting occur from respiratory or heavy dermal exposure. Indeed, a Chinese chemical warfare analyst has classified lewisite as a vomiting agent (Fang, 1983). In both people and animals, the vomiting is associated with retching, such that humans might remove protective masks. The retching appears to be distinctive, unlike the more common symptoms of nausea and vomiting (Sidell, Takafuji, and Franz, 1997; Vedder, 1925). In contrast to what might be expected, there is no documentation of liver effects from chronic exposure.

There are no specific musculoskeletal findings, although weakness has been observed. There is little clinical information about effects on bone marrow and the immune and endocrine systems. Renal disorders, although theoretically possible, are not described.

There is no substantial evidence that lewisite is carcinogenic, teratogenic, or mutagenic (Dacre, 1989; Sidell, Takafuji, and Franz, 1997, p. 220).

What to Look for in the Gulf Context

If lewisite exposures occurred during the Gulf War, they must have been relatively mild to have escaped recognition. The setting in which Fox vehicles detected lewisite—near a breaching operation—was a possible situation for lewisite exposure; however, alternative explanations have been given for the readings, mainly that the Fox vehicle's road wheels, which are made of silicone, can off-gas, which results in false lewisite readings (OSAGWI, 1997c). The UN has not reported finding lewisite in the destroyed Iraqi chemicals (UNSCOM, 1991, 1992, 1995).

No clinical cases have been associated with the reports of lewisite detection from Fox vehicles during the Gulf War. The matter has been extensively evaluated, and the reports appear to have been in error, reflecting massive contamination from oil fire products and a misidentification of materials in the system (OSAGWI, 1997c; OSAGWI, 1997e).

It is possible that low-level exposures to lewisite could have resembled common eye irritation and respiratory infections. Clinical association of eye and

respiratory symptoms with nausea vomiting and retching might be a clue that lewisite was the cause. Should there be further concern about lewisite exposure in the Gulf, some effort to correlate epidemiological data with tactical events might be useful. It is not likely that lewisite could produce vomiting without eye and skin effects.

If mask filters or other equipment from the war become available, measurements of residual arsenic might document lewisite use. It should be noted that arsenic is present in nature in some soils and waters, so its presence alone would not be solid proof of lewisite use. Since the half-life of arsenic in body tissues is days to weeks, there does not appear to be any merit in measuring arsenic levels in Gulf veterans so long after the possible exposure.

Summary and Conclusions

There is no strong reason to think that U.S. forces experienced a lewisite attack or that lewisite was in the Iraqi arsenal. A real attack would have been hard to overlook. Such an attack would produce blisters, eye injuries, and associated severe vomiting and retching. A small-scale accidental low-level release near U.S. forces could have produced eye and respiratory symptoms that could have been misdiagnosed as routine eye irritation and respiratory infections.

The information on the long-term consequences of lewisite exposure is not extensive. There is no indication that brief low-level exposures are associated with long-term problems. Arsenic can cause polyneuropathy, but there is no documentation of this occurring in humans or animals after acute arsenic-containing lewisite exposure. More chronically exposed munitions workers developed sustained bronchitis but apparently not neuropathy. There is reason to think chronic exposure may predispose to Bowen's squamous cell intraepithelial cancer. There is, however, no indication of the presence of enough lewisite to produce chronic exposures during the Gulf War.

PHOSGENE OXIME

Phosgene oxime (also known as CX, or dichloroform oxime) belongs to a class of chemical warfare agents known as urticants or nettle gases, so named because of their property of intensely irritating the skin immediately after contact. Shortly after skin exposure and initial irritation, erythema, severe itching, hives, and painful blisters that resemble nettle stings develop. The symptoms spread far beyond the region of initial exposure (Franke, 1967). Fatal pulmonary edema has been produced in experimental animals 2 to 24 hours after percutaneous exposure to liquid phosgene oxime. Phosgene oxime is also classified as a vesicant, unlike phosgene, which is a choking agent. Very little is known about the pathophysiology of phosgene oxime intoxication.

Phosgene oxime is an unlikely candidate for a cause of illnesses in Gulf War veterans. UNSCOM has not reported this agent in the Iraqi chemicals they destroyed; the agent is so aggressive that its use would be hard to overlook (UNSCOM, 1991, 1992, 1995). There were indications of Iraqi use of an agent whose effects resembled phosgene oxime against Iran (OSAGWI, 1990), but confirmation is lacking.

History

Phosgene oxime's chemical properties have been known since the late 1920s; researchers Prandtl and Sennewald synthesized it in 1929 (see AD Little, 1986, Ch. 3). Germany, the Soviet Union, and other countries appreciated its military potential, once storage and stability problems were addressed. Major powers stockpiled this agent during World War II, although there is no record of its use (SIPRI, 1971; SIPRI, 1973).

Several German sources (Rebentisch, 1980; Franke, 1967; Hirsch, 1950; Hackman, 1934) indicate that there was interest in the agent, whose immediate incapacitating effects were notable; it was also mixed with lewisite and mustard. Hackman, an advisor on the agent's use, commented that "there are few substances in organic chemistry that exert such a violent effect on the human organism as this compound." However, neither Malatesta et al. (1983) nor Wells and MacFarlan (1938) found the respiratory toxicity in animals to be impressive and judged the vesication responses to the dilute agent to be inferior to mustard. There was initial concern that phosgene oxime, because it attacks rubber, might impair the effectiveness of mask canisters, some of which emitted smoke when exposed to phosgene oxime. Later studies, however, did not support this concern (Goshorn et al., 1956).

No detectors have specifically been configured to detect phosgene oxime, and it was difficult to locate information on its detection. Sidell, Takafuji, and Franz (1997), pp. 220–222, indicated that the M256A1 detector can detect phosgene oxime. This may be a reference to the paper detectors. The authors provided no sensitivity data. However, OSAGWI informed RAND that the M256A1 detector uses the blister test to detect phosgene oxime and responds to levels between 3 and 5 mg/m³ and that it is possible to program the MM1 detector in the Fox vehicle to detect phosgene oxime.

Weaponization

Phosgene oxime might be delivered by artillery or rockets as a "surprise" agent combined with other chemicals (e.g., smokes or nerve agents) to produce prompt incapacitation and then death in antiarmor or air-defense crews. The pain from phosgene oxime on the face might cause removal of protective

masks, while the corrosive effects on the skin might render it more vulnerable to penetration by nerve agents (Franke, 1967; Sidell, Takafuji, and Franz, 1997, pp. 220–222). The extreme irritation and immediate eye injury and later lung injury would also be of military significance (Rebentisch and Dinkloh, 1980; AD Little, 1986, Ch. 3). No information is available about Iraqi views on phosgene oxime (Sidell, Takafuji, and Franz, 1997; U.S. Army, 1990). There is a report that Iraq used a chemical agent on several occasions during the war with Iran, which could not be confirmed. Other reports referred to use of “phosgene,” and described eye and skin effects, such as immediate eye irritation, immediate pain, and pallor of spots on exposed skin within 30 seconds, evolving into an open wound within one week. These are all symptoms of exposure to phosgene oxime (OSAGWI, 1990).

Toxicology and Toxicokinetics

Table 3.3 summarizes the structure and physical and chemical properties of phosgene oxime. It may persist in soil for two hours but does not persist on materiel. Water decontaminates it on skin (Sidell, Takafuji, and Franz, 1997, pp. 220–222).

The primary exposure routes for phosgene oxime, when used as a chemical warfare agent, are mucous membranes (eyes, nose, and throat) and the skin. Enough phosgene oxime can be absorbed through the skin to produce systemic poisoning and death, especially if the agent is liquid. The delayed pulmonary toxicity from percutaneous or parenteral exposure is not unique and is similar to effects of phosgene, phorbol, and combustion products.

Mechanisms of Action

While there are many interesting theories about the mechanism of action, recent studies provide no proof. It has not been established whether the toxicity arises from the necrotizing effects of hydrochloric acid liberated during hydrolysis, from the direct effects of the oxime, or from the carbonyl grouping. Delayed pulmonary effects from injection indicate a mechanism other than the direct effects of hydrochloric acid. Taylor (1983) suggested the likelihood that the agent has a bifunctional effect deriving from alkylating and nucleophilic properties. He suggests the alkylating properties might resemble those of mustard. No data on metabolism of phosgene oxime have been found. Sidell, Takafuji, and Franz (1997), pp. 220–222, note that the cellular targets of phosgene oxime are unknown but indicate that there are two main paths of injury:

1. **direct**—involving enzyme inactivation, corrosive injury, and cell death with rapid tissue destruction

2. **indirect**—involving activation of alveolar macrophages, recruitment of neutrophils, and release of hydrogen peroxide, resulting in delayed tissue injury, such as pulmonary edema.

Exposure-Effect Relationships

Lethal systemic doses of phosgene oxime for humans have not been determined, but estimates are in the range of 30 mg/kg. Other reported human-effect thresholds vary from 1 mg/m³ for irritation from older German reports (Franke, 1967) to a more recent 3 mg/m³ for irritation and 1 mg/m³ for detection (Malatesta et al., 1983). The minimum effective respiratory dosage is estimated to be a CT of 300 mg/m³, while the lethal dose that kills half the exposed

Table 3.3
Chemical and Physical Properties of Phosgene Oxime

Agent	Phosgene oxime CX Dichloroformoxime
Chemical structure	$\begin{array}{c} \text{Cl} \\ \diagdown \\ \text{C} = \text{N} - \text{OH} \\ \diagup \\ \text{Cl} \end{array}$
Molecular weight	113.94
Physical state (20°C)	Yellowish-brown liquid (munitions-grade) or colorless, crystalline solid (pure). When cooled, pure solid turns pink on long standing; less pure material gives light yellow slurry.
Vapor density (compared to air)	3.9
Liquid density (g/cc)	Not found
Boiling point (°C, 760 mm hg)	129° (decomposes)
Melting point (°C)	35–40° (pure)
Vapor pressure (mm hg)	13 at 40°C
Volatility (mg/m ³)	1,800 at 20°C; 76,000 at 40°C (evaporates readily)
Viscosity (cp at 20°C)	Not found
Surface tension (dynes/cm at 20°C)	Not found
Solubility	Readily soluble in water; very soluble in organic solvents
Decomposition temperature (°C)	<128
Odor	Disagreeable, prickling odor

SOURCE: AD Little (1986, Ch. 3), U.S. Army (1990).

population (LCT₅₀) is 3,200 (which is about twice the LCT₅₀ of mustard) (Sidell, Takafuji, and Franz, 1997, pp. 220–222; U.S. Army 1990; AD Little, 1986, Ch. 3).⁶

Human responses vary with increasing phosgene oxime skin concentrations. There was slight irritation from a 1-percent solution after 24 hours (Wells and MacFarlan, 1938). In one subject, intense itching and a raised red nodule developed, surprisingly, 11 days after such an application. Malatesta et al. (1983) found moderate erythema in four of six volunteers after exposure to a 1.5 percent solution, and three of six exposed to a 2-percent solution developed intense erythema and itching with vesicles a few hours later. All subjects exposed to a 3-percent phosgene oxime solution developed intense erythema and vesicles. A 70-percent liquid exposure produced an intense reaction, with skin damage (McAdams and Joffe, 1955). No information about sustained low-dose exposures, as might have occurred in munitions production, has been found; neither have other reports of delayed reactions.

There is no information about drug and environmental chemical interactions with phosgene oxime. McAdams and Joffe (1955) found that methenamine pretreatment, which was used in U.S. Army munitions plants to protect workers from phosgene, did offer some protection.

Clinical and Pathological Findings

No standard descriptions are available, and symptoms vary depending on the route, form (vapor or liquid), and dose of exposure. In the case of vapor, immediate eye and respiratory irritation are expected, with coughing, throat pain, increased lachrymation, keratitis, and impaired vision (Franke, 1967). Systemic effects, including headache and anxiety, may occur later. Hypersensitivity reactions to mustard agents have been described (Daughters et al., 1973); because phosgene oxime has alkylating properties and is able to bind to proteins, it is theoretically possible that it could serve as a hapten in creating some autoimmunity. There are no definitive laboratory studies of phosgene oxime, although some experimental data are available (Mol and Wolthuis, 1987). The effects of phosgene oxime, especially on the skin, resemble those of strong acids. Its effects are greatest on the first capillary bed encountered, e.g., cutaneous or intravenous exposures cause pulmonary edema, while portal-vein injection causes liver necrosis but spares the lung (McAdams and Joffe, 1955; Sidell, Takafuji, and Franz, 1997, pp. 220–222).

Skin. There is immediate severe itching and pain after exposure to higher concentrations of liquid phosgene oxime, lasting 30 minutes to three hours (Hirsch,

⁶CT is measured in milligrams per minute per cubic meter. Appendix A explains CT, LCT, etc., dosages.

1950; Franke, 1967; AD Little, 1986, Ch. 3). A pale translucent area surrounded by erythema may develop at the site of contact, with hives forming in about 10 minutes. As the itching spreads, a rash may also appear in unexposed areas, suggestive of the action of substance P, a mediator that acts locally and on dorsal root ganglia. Pain lasts three to four hours but may recur for several days if the affected area is moistened or irritated. Subsequently, the skin lesion forms an eschar that may be deep, pitted, and slow to heal (Franke, 1967; Malatesta et al., 1983; McAdams and Joffe, 1955; Joffe, et al., 1954; Wende, 1977). Secondary infections are common, and complete healing may take one to two months.

Histologically, phosgene oxime lesions show a through-and-through injury extending into underlying panniculus and muscle with a polymorphonuclear infiltrate at the margins. Congestion and hemorrhage accompany thrombosis in small arteries and veins.

Eye. The eye effects appear similar to those of lewisite, with pain, tearing, conjunctivitis and keratitis. There is no information about the longer-term course of these injuries. Alexandrov, a Soviet scientist, has stated that phosgene oxime can cause blindness at low levels but has not been explicit about quantities and does not provide histological data (AD Little, 1986, Ch. 3).

Respiratory. Death in animals requires high concentrations, even though respiratory irritation occurs at lower levels. Tachypnea, dyspnea, and cyanosis would be expected to occur if pulmonary edema arises. Aerosol exposures produce necrotizing bronchiolitis and pulmonary edema, with pulmonary vein thrombosis (Petersen, 1965). Although phosgene oxime skin lesions are prone to secondary infections, it has not been documented that pulmonary infectious complications are common. Rats exposed to sublethal doses of phosgene were predisposed to increased severity of influenza (Ehrlich and Burleson, 1991).

Long-Term Effects. There are no long-term respiratory injury data, although pulmonary fibrosis could develop, as it does with some alkylating agents, such as bleomycin. Information about long-term eye and skin effects is also lacking. If concern about possible Gulf War exposure increases, the German government may be able to provide information from studies of exposures of World War II munitions workers (Lohs, 1975). It seems possible that phosgene oxime, like mustard, might induce hypersensitivity, perhaps by serving as a hapten linked to proteins encountered. There is one reported case of a delayed skin response to phosgene oxime (Wells and MacFarlan, 1938).

What to Look for in the Gulf Context

Had phosgene oxime exposures from proximate weapon release occurred, there should have been reports of severe eye and respiratory irritation with dermal

stinging and itching. The respiratory symptoms would resolve fairly rapidly, but eye and skin problems would last longer. Long-term pulmonary problems from mild exposures are unlikely. Although late effects from symptomatic exposures cannot be ruled out, had pulmonary edema occurred from any Gulf War exposure, it would not have escaped attention. There do not appear to have been any false-positive phosgene oxime reports during the war. Liquid or droplet exposures would have produced painful, slow-healing lesions, which patients and caregivers would recall, although the effects of the mildest exposures might seem nonspecific. Here again, it is not possible to exclude long-term effects entirely. Thus, it might be useful to create a picture of the dermatological problems seen in troops during and after the Gulf War (and not just those for phosgene oxime).

Although there were unverified reports of the use phosgene oxime several times during the Iran-Iraq War (OSAGWI, 1990), no events during the Gulf War raised serious questions about its use. Its presence was suspected in one instance, at a girls' school in Kuwait after the war, but later disproven. The school had been used by Iraqi forces that left a tank of liquid behind. Fumes that came from the tank were investigated and liquid from the tank wet the protective ensemble of a coalition officer, who sustained a prompt and painful burning injury of his skin. This caused phosgene oxime to be suspected. It was later shown that the liquid was some kind of nitric acid, a missile propellant, and the injury was an acid burn (OSAGWI, 1998a).

Summary, Conclusions, and Recommendations

Exposure to phosgene oxime liquid, vapor, or aerosols would be expected to produce immediate eye and respiratory irritation and skin pain. Typical skin burns would require attention and would heal slowly. The literature does not suggest profound central nervous system problems. Phosgene oxime has not been well studied, and its mechanisms of action are not understood. No information about low-level and chronic effects exists, but it is not possible to rule out delayed effects. Phosgene oxime is highly reactive and volatile, so it is unlikely to produce persistent environmental hazards or to survive long-distance environmental transportation from remote release. It is nonpersistent (Franke, 1967). There is no information proving Iraqi phosgene oxime possession, and the experiences recounted in congressional testimony and elsewhere are not consistent with phosgene oxime exposure.

If phosgene oxime continues to be a threat agent, more research will be needed to determine its mechanisms of action and to improve prevention and therapy, particularly if reasons to suspect low-level sustained exposures in Gulf War personnel emerge. Inquiries should then be made about the health and experi-

ences of production workers in countries that have produced military amounts of phosgene oxime.

MUSTARDS

The mustard agents are a family of sulfur-, nitrogen-, and oxygen-based compounds with similar chemical and biological effects (OSRD, 1946; Franke, 1967; U.S. Army, 1990). This review focuses on sulfur mustard (H), or Levinstein mustard, the compound Iraqi forces were most likely to have used, although the more stable distilled mustard (HD) may have been available.

Other potent sulfur-based mustards (Q and T) have been found in small amounts in Iraqi mustard from weapons used in Iran (UN, 1984). These agents have also been placed in U.S. chemical weapons. Agent T is a more potent vesicant than H and is more stable, with a lower freezing point. Agent T has been incorporated into U.S. agent HT (HD+T) and is two to three times as toxic as H. However, it has a lower vapor pressure than H, making it inefficient as a vapor (U.S. Army, 1990; Franke, 1967; Karakchiev, 1973; UN, 1984). Agent Q is a potent vesicant and lung-injuring agent (more so than H) but has a very low vapor pressure, so it is not much of a respiratory threat except in aerosol form.

Nitrogen mustard is poorly soluble in water but highly soluble in organic solvents. This agent (as Mustargen[®]) is used in cancer chemotherapy for a variety of conditions, including Hodgkin's lymphoma (PDR, 1998).

Mustards produce slow-healing injuries to the eyes, respiratory tract, and the skin. They have potentially lethal systemic effects and produce late long-term effects after substantial exposures (Vedder, 1925; Papirmeister et al., 1991; U.S. Department of Health and Human Services, 1992; Wachtel, 1941; Watson and Griffin, 1992; Smith and Dunn, 1991; Smith et al., 1995; Dacre and Goldman, 1996; Sidell, Takafuji, and Franz, 1997, pp. 198–217).

History

Sulfur mustard (see Table 3.4) was synthesized before World War I and was known to be toxic (Wachtel, 1941). It was effectively used in World War I, first by the Germans and later by the Allies. Mustards had low lethality (1 to 6 percent) but produced incapacitating eye, respiratory, and skin injuries, disabling thousands for short or long periods. Mustards were persistent; hard to detect; and, because of the skin injuries, dangerous even to troops wearing protective masks. Psychologically, they precipitated exhaustion, chronic anxiety, and poor morale (Vedder, 1925). These agents accounted for 10 percent of all man-days lost by U.S. forces in France and for 77 percent of the British chemical casualties (Vedder, 1925; Gilchrist, 1928).

Table 3.4
Chemical and Physical Properties of Sulfur Mustard

Agent	Sulfur mustard Hs Bis-(2-chloroethyl) sulfide Yperite Levinstein mustard Lost Senfgas
Chemical structure	$\begin{array}{l} \text{S} \begin{array}{l} \diagup \text{CH}_2\text{CH}_2\text{Cl} \\ \diagdown \text{CH}_2\text{CH}_2\text{Cl} \end{array} \end{array}$
Molecular weight	159.08
Physical state (20°C)	Oily, colorless (pure) to yellowish dark-brown (munitions-grade) liquid
Vapor density (compared to air)	5.4–5.5 (hovers near ground, settles in depressions)
Liquid density (g/cm ³)	1.262–1.2741 at 20°C
Boiling point (°C, 760 mm Hg)	227.8 (decomposition calculated at 216°C)
Freezing point (°C)	13–14.4
Vapor pressure (mm Hg at 20°C)	0.06–0.11
Volatility (mg/m ³ at 20°C)	610 (liquid); 625
Viscosity (cp at 20°C)	4.59
Surface tension (dynes/cm at 20°C)	42.8
Solubility	Slightly soluble in water (0.7–0.92 g/l at 22°C); miscible in most organic solvents
Decomposition temperature (°C)	149–177
Odor	Almost odorless in pure state at typical field concentrations; horseradish, garlic, or mustardlike odor at higher concentrations

SOURCES: U.S. Army (1990), Vedder (1925), Wachtel (1941), Karakchiev (1973), Franke (1967), Dacre and Goldman (1996).

In World War II, all major combatants produced mustard, and much of what is known of long-term effects comes from studies of World War II munitions workers. Research exposing large numbers of troops was performed (Pechura and Rall, 1993). Although mustards were not operationally used during the war, one large release resulted from a German air attack on Bari, Italy. The 16 ships sunk during the attack included a U.S. freighter carrying 100 tons of mustard. Several thousand mustard casualties occurred, including many deaths. Several ships burned, and some mustard may have been spread by smoke from the oil fires, since casualties occurred in ships offshore (Infield, 1971; Dacre and Goldman, 1996).

Iraqi forces used mustards against Iranian forces beginning in 1984 and continuing through the war (Cordesman and Wagner, 1990; UN, 1984). Some Iranian casualties were cared for in western European medical centers, resulting in many clinical reports (Heyndrickx, 1984). Most Iranian chemical casualties were caused by mustard.

A novel feature of Iraq's use of mustard against Iran included mustard that was adhered to fine (0.1 to 10 μm) silica particles, in a mixture of 65 percent mustard and 35 percent silica. This combination produced more-serious respiratory injuries than other forms of mustard and a different form of skin injury, with symptoms beginning in 15 minutes to one hour (as opposed to four to eight hours). A fine rash with multiple small dots was produced, progressing to vesication with darkened skin and peeling of the epidermis after several days (OSAGWI, undated a). Before the Gulf War, it was uncertain whether U.S. systems would be able to detect dusty mustard or nitrogen mustard and whether such particles could penetrate protective clothing (U.S. Army XVIII Corps, 1998). Coalition forces apparently did not encounter this agent, and it is not mentioned in the UNSCOM reports of 1991, 1992, or 1995. We were unable to locate reports of laboratory studies of the effects of mustard in this form.

Weaponization

Mustard is attractive for military use because

1. Its potency is fairly high (five times that of phosgene).
2. It is able to inflict casualties despite use of respiratory protection.
3. Detection by odor is unreliable, although toxic levels can be noted (Smith, Hurst, et al., 1995)
4. It causes delayed effects, producing no signs or symptoms until irreversible injury is inflicted.
5. It causes prolonged disability.
6. It is stable in storage and persistent in the environment.
7. It is easy and inexpensive to produce.
8. It is difficult to decontaminate.
9. It penetrates many materials.
10. It mixes well with other chemical agents.
11. It can be used in vapor form (denser than air).
12. It can be used in aerosol form, permitting large-area and off-target attacks.
13. It can be used in liquid form, permitting long-term denial of terrain, facilities, and equipment.

Mustard is readily delivered by mortar rounds, artillery, free rockets, aerial bombs, aerosol spray tanks, and liquid spray tanks. Its tendency to freeze with aerial delivery can be reduced by mixing with lewisite or nerve agents or other solvents. In artillery rounds, effective amounts can be delivered using explosive charges equal to ordinary rounds, thus concealing the use of chemicals (OSRD, 1946). Iraq used aircraft and artillery to deliver mustard during its war with Iran.

The press mentioned that Iraq might have intended to contaminate oil-well fires and smoke with chemicals (OSAGWI, 1998; Spektor, 1998). High temperatures destroy mustards, but the Bari experience suggests toxic smokes are possible (Franke, 1967; Wachtel, 1941; Vedder, 1925; OSRD, 1946; SIPRI, 1971; U.S. Army, 1990; Infield, 1971).

Operationally, mustard is usually a defensive agent, creating barriers against attacking forces and complicating their operations by requiring protective systems. After the build-up of coalition forces, the situation favored Iraqi defensive use of mustards (SIPRI, 1971; SIPRI, 1973).

Gulf Relevance

When coalition forces deployed to the Gulf in 1990, there was concern that Iraq might use mustard agents. No large-scale use was encountered, but there were scattered reports of detection alarms, and at least one U.S. soldier developed skin lesions typical of mustard after being in an Iraqi bunker (OSAGWI, 1997d).⁷ During the air war, at least two targets containing mustard (and sarin) were hit—both in remote areas west of Baghdad (Muhammadiyah and Al Muthanna). Iraq declared to the UN that 200 mustard-filled and 12 sarin-filled bombs were destroyed at Muhammadiyah. Only 5 percent of Iraqi chemical stores appear to have been destroyed by bombing. CIA calculations of agent dispersal from these attacks indicate that they did not yield significant concentrations of agents in the vicinity of U.S. forces, which were some 400 km away (CIA, 1996). Artillery shells containing mustard were present at Khamisiyah. They apparently escaped destruction by U.S. demolitions (OSAGWI, 1997a).

Low-level exposures might have produced mild and nonspecific responses. However, releases sufficient to have a biological effect on many personnel would lead to some inequality in exposures, such that some typical lesions would be recognized. The extensive human experience with mustards has not produced large numbers of cases with high similarities to illnesses in Gulf War veterans, but some less-well-studied neurobehavioral and skin problems are

⁷According to an interview in *Army Times*, this soldier is experiencing long-term health problems; he is quoted as having problems with memory and concentration which began after his return to the United States (Funk, 1997).

discussed later. There is controversy about detector reports that cannot be resolved here.

Detection

Humans can detect the odor of mustard (or associated chemicals), although unreliably. The smell is described as resembling garlic or mustard—differing from the geranium smell associated with lewisite (Sidell, Takafuji, and Franz, 1997, p. 198). Field items that are part of the M256A1 detection kit can colorimetrically detect mustards (e.g., M8 paper). The UK's Chemical Agent Monitor (CAM) detects mustard using an ion mobility spectrometer, and the Fox vehicle has a mass spectrometer (note that there are concerns about detection of dusty agent). Other laboratory techniques may be used including gas chromatography and flame photometry.

The detection and monitoring of exposure to mustards and other alkylating agents have been well studied. Gas chromatography and mass spectroscopy can demonstrate the presence of mustard adducts in DNA at the level of 10 picomoles (Ludlum and Austin-Ritchie, 1994). Immunochemical (monoclonal) and mass spectroscopy can now detect sulfur mustard adducts (Noort et al., 1996). Other tissue detection of mustards and alkylating agents is based on adducts with hemoglobin and was used to confirm nonterminal valine adducts of hemoglobin in red blood cells from Iranian casualties (Ehrenberg and Osterman-Golkar, 1980; Hoffman, 1998).

Thiodiglycol, a chemical resulting from sulfur mustard hydrolysis (see next section), can be detected in the urine and indicates exposure. Tests for thiodiglycol have been positive in Iranian casualties and in laboratory accident cases (OSAGWI, 1997d). In the one U.S. Gulf mustard casualty (OSAGWI, 1997d; Sidell, Takafuji, and Franz, 1997), there is uncertainty. One early urine test was reported as positive, but a repeat study at a U.S. laboratory did not confirm. The small size of the injury would make detection difficult (OSAGWI, 1997d).

Discussions with AFIP indicate it has registries of tissue from the Gulf period and material from fatalities in the United States after return. It should be possible to detect evidence of mustard in blood and tissues taken within a few months after suspected exposures.

The structure of nitrogen mustard (Figure 3.1) resembles that of sulfur mustard. There are some other nitrogen-based mustards. The one shown in Figure 3.1 is still used in cancer therapy.

Sulfur mustard, when it hydrolyzes in the water of biological fluids, produces hydrochloric acid and thiodiglycol, the latter of which can be detected in fluids and urine and is relatively nontoxic (Figure 3.2). Chlorination is effective in destroying mustard but the reaction is highly exothermic (Lohs, 1975).

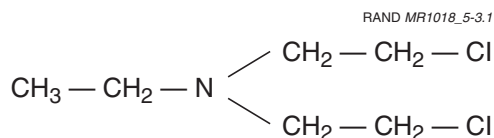


Figure 3.1—Structure of Nitrogen Mustard

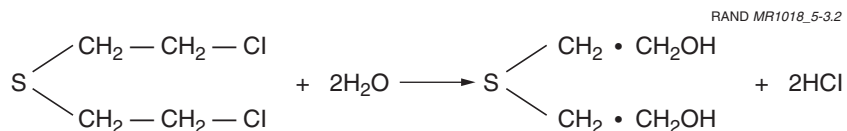


Figure 3.2—Hydrolysis of Sulfur Mustard

Mechanism of Action

There is a large body of literature on the biochemical interactions of mustards, stimulated in part by interest in their application to cancer chemotherapy. Public health considerations arising from demilitarization have focused on lower-level effects and longer-term consequences, in an effort to establish safety standards (U.S. Department of Health and Human Services, 1992).

Although clinical manifestations of mustard injury are slow to appear, the initiating events occur rapidly. It appears that mustard is actively transported across the cell membrane using a system involved in choline transport.⁸ Mustards probably are not metabolized in the usual sense by enzymatic degradation. Instead, they form highly reactive chemical species that alkylate macromolecules, most importantly DNA in the cell nucleus. Rapidly dividing cells are most sensitive to these effects, accounting for the similarities between mustard and radiation injuries, with mustards being characterized as radiomimetic agents. Although dividing cells are sensitive, mustards at significant concentrations kill cells whether dividing or not.

Mustards produce several forms of highly reactive compounds. Among these are carbonium ions, which react readily with nucleophilic entities within the cell. The two side chains in mustard favor the insertion of alkyl groups into other molecules (alkylation), which is the most important factor in the biologi-

⁸Some resistant cell lines do not transport mustards well (Goldenberg et al., 1970; AD Little, 1986, Ch. 2).

cal effects of these agents (Karakchiev, 1973; Dacre and Goldman, 1996; Papirmeister et al., 1985).

Nucleophilic guanine moieties of the DNA helix permit alkylation and subsequent cross-linking of the strands, impairing the ability of the DNA to divide and be “read” for translation by RNA. Mustard-resistant bacteria have the ability to repair damage by excising the cross links, but mammalian cells cannot do this. Mustards cause cell death through chromatin condensation and energy loss following DNA breakage, loss of cell membrane integrity, or perturbation of cytoskeletal organization (Smith et al., 1995). Induction of programmed cell death, or apoptosis, has also been demonstrated (Hinshaw et al., 1996). The longer-term consequences of DNA alkylation are reflected in mustards’ mutagenicity and carcinogenicity (Brookes, 1990).

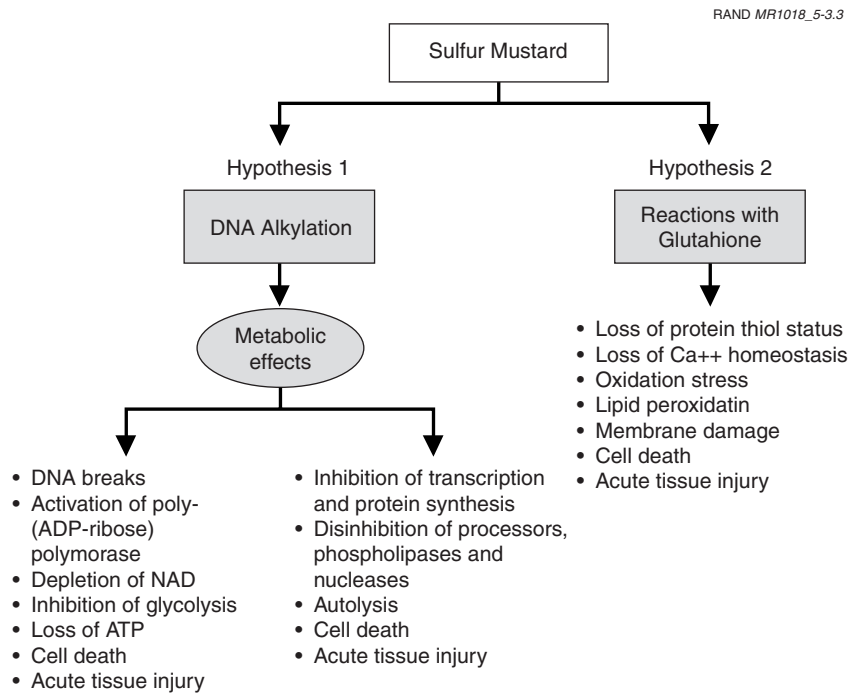
The stage in the cell cycle at which division occurs (G stage) is the most sensitive for mustard effects, while the S-stage cells seem more resistant. Tissues with high cell turnover (e.g., bone marrow, intestinal epithelial cells, and some skin elements) are especially sensitive to mustards because a higher percentage of cells is dividing (Meyn and Murray, 1984).

The main effects of DNA alkylation and reactions with glutathione set in motion a cascade of effects that includes depletion of cell energy by activation of DNA repair mechanisms (Watson and Griffin, 1992; Papirmeister et al., 1985, 1991). Cell membranes may be directly or secondarily affected by glutathione depletion, with alterations of cytokine activity (Smith et al., 1995; Dannenberg et al., 1985; Gross et al., 1985; Papirmeister et al., 1985). Although not all mechanisms have been established conclusively, Figure 3.3 shows the putative multiple mechanisms for tissue damage from mustards.

The mustards also directly bind to biological materials other than DNA (e.g., cell membranes, proteins). Mustards react with the active portions of enzymes, such as hexokinase, pyruvate oxidase, creatine kinase, ATPase, and acetylcholinesterase (AChE), with subsequent loss of enzyme function (Karakchiev, 1973; OSRD, 1946; Vojvodic et al., 1985; Krustanov, 1962). Dacre and Goldman (1996) summarized several reports of irreversible inhibition of AChE by mustard.

Krustanov (1962) showed that, in rabbits, 10 mg/kg of mustard on the skin lowered serum cholinesterase by 33 percent, an amount similar to 0.4 mg/kg of tabun subcutaneous.

Another alkylating agent, cytoxan, inhibits AChE in clinically significant ways; anesthesiologists must be warned if succinylcholine is planned within ten days of using cytoxan [PDR, 1998].



SOURCE: Reprinted with permission from Sidell, Takafuji, and Franz (1997), p. 202.

Figure 3.3—Sulfur Mustard's Putative Tissue-Damaging Mechanisms

Metabolism and Distribution

Until recently the common view has been that mustards were not metabolized by enzymatic processes, although they did hydrolyze in biological tissues (see below) (Sidell, Takafuji, and Franz, 1997). Their effects accumulated as a result of binding to critical structures.

An enzyme, thioethermethyl transferase (TGMTase), was identified in mice in 1986 and has now been shown via recombinant methods to be present at least in human livers. The enzyme methylates and thereby inactivates the S atom on mustard agents. It may provide some endogenous protection from mustard agents, although quantitative data are not available (Hoffman, 1998).

As noted previously, sulfur mustard hydrolyzes to thiodiglycol and hydrochloric acid. The high reactivity of mustards causes binding to sulfhydryl groups, which serve to detoxify the agents, as in the case of glutathione systems. Studies in a variety of species, including humans, have shown conjugates with glutathione in the urine, reflecting alkylation, rather than enzymatic action. Other

products were thiodiglycol, conjugates of thiodiglycol with glutathione, and conjugates of bis-beta-chloroethylsulfone with glutathione or cysteine (Dacre and Goldman 1996).

Radioactively labeled mustard given intravenously to rabbits disappeared rapidly from the circulation, with much of the label appearing in urine and bile within 20 minutes, with a small remainder widely distributed, especially to liver, kidney, and lungs. How much of this represents metabolism by TGMTase, conjugation with glutathione, or hydrolysis is not known. Findings from intravenous administration to cancer patients were similar, with immediate disappearance of 90 percent of the label from blood and only a small amount residing on plasma proteins (Dacre and Goldman, 1996).

Because they are lipophilic, mustards readily penetrate the skin. Liquids or saturated vapor are absorbed at a rate of 1 to 4 $\mu\text{g}/\text{cm}^2/\text{min}$, indicating the importance of the total area of exposure (Papirmeister, 1991; Dacre and Goldman 1996). It takes about 10 minutes for mustard to penetrate the skin, with 12 percent being fixed in the skin and 88 percent disappearing rapidly from the circulation (Dacre and Goldman 1996). No technical studies of dusty mustard on the skin appear to be available. The rapid development of symptoms raises the possibility that the silica particles are capable of penetrating the stratum corneum of the skin, which ordinarily delays the passage of chemicals.

Although mustard exposure appears to have neurological consequences, the detailed distribution to the brain has apparently not been reported thus far. Vojvodic et al. (1985) did not find decreases in AChE in the brains of animals exposed to mustard. Lipophilic materials generally are well distributed to the brain. Scremin et al. (Scremin, Shih, and Corcoran, 1991; Scremin and Jenden, 1996) have noted that regional blood flow to the brain reflects regional brain activity, with the probability that lipophilic agents would be preferentially distributed to neurologically and metabolically active sites in the brain.

This raises the possibility that brain activity at time of exposure might significantly influence distribution of lipophilic agents to the brain, such as mustards and nerve agents.

Effects of Exposure and Exposure Limits

Table 3.5 summarizes the quantitative aspects of the exposure-effects relationships for various regions of exposure (Lethal figures for humans are estimates). In general, there is little information about sustained low levels of exposure. McNamara et al. (1975) report no mortality, but tumor prevalence increased in four animal species exposed to 0.1 mg/m^3 for a year. Dacre and Goldman (1996) give a no-effect exposure level for rats of 0.1 mg/kg , taken orally for 90

Table 3.5
Effects of Exposure to Mustards (H or HD)

Area	Dose ^a	Effect ^b	Time of Effect Onset	Sources
Eyes	<5	None		McNamara et al. (1975)
	12	Irritation, reddening	Hours to days	Karakchiev (1973), Dacre and Goldman (1996)
	30–70; 50–100	Conjunctivitis, tearing, photophobia	4–12 hours	AD Little (1986), Wachtel (1941), McNamara et al. (1975)
Respiratory	100–200	ICT ₅₀ (est.), corneal edema, lid edema, corneal ulceration	3–12 hours	U.S. Army (1990), Wachtel (1941), OSRD (1946)
	33–70	Irritation of nasal mucosa	12 hours–2 days	Wachtel (1941), OSRD (1946)
	100	Severe effects		NAS (1997)
	150	ICT ₅₀ , sneezing, lachrymation, nose bleed, sore throat		U.S. Army (1990)
	133–600	Tracheobronchitis, cough, pseudomembrane, fever	4–6 hours	OSRD (1946)
	390–900 900	Serious lung injury, pulmonary edema, pneumonia Revised LCT ₅₀	4–6 hours	Wachtel (1941) NAS (1997)
Skin (vapor)	1,500	LCT ₅₀ , respiratory failure, delayed death	4–6 hours	U.S. Army (1990)
	15–150	Erythema, threshold effect	Hours to days	AD Little (1986)
	25–50	Erythema, threshold effect	Hours to days	NAS (1997)
	75–300	Skin injury	Hours, days	AD Little (1986), OSRD (1946)
	450	Injury with large blisters	Hours	Vedder (1925), OSRD (1946)
	500	Severe effects (<200 hot temp)		NAS (1997)
	600	Sustained vomiting		Wachtel (1941)
	1,000–2,000 5,000 10,000	Incapacitating skin injury Revised LCT ₅₀ LCT ₅₀	Hours 3 hours	U.S. Army (1990) NAS (1997) U.S. Army (1990)

Table 3.5—Continued

Area	Dose ^a	Effect ^b	Time of Effect Onset	Sources
Skin (liquid)	610 mg ^c	ED ₅₀ , severe effects ^d		NAS (1997)
	1,400 mg ^c	LD ₅₀		SIPRI (1973).
	4,000–7,000 mg ^c	LD ₅₀		SIPRI (1973), U.S. Army (1990)
	60 mg/cm ²	Lethal dose (est.)		NATO (1983)
Miscellaneous	480	Impaired military efficiency		Wachtel (1941)

^aCT (in mg·min/m³) unless specified otherwise.

^bVapor or aerosol.

^cFor a 70 kg person.

^dED stands for “effective dose.”

NOTE: There are considerable variations in the data that the reviewer cannot readily explain. They may reflect differences in experimental design, extrapolations from animal studies, temperature, and individual variations. Eye and respiratory systems have similar sensitivities, but eye effects have shorter latency (Somani, 1992, p. 54).

days. Troops on World War I battlefields endured sustained exposure at times, but the levels are unknown, as is also the case for occupational exposures from that period. The judgment of International Agency for Research on Cancer that mustard is a carcinogen seems well founded on the basis of animal research and human epidemiology studies.

Exposure standards are as follows: For H, HD, and HT, the concentration limit for workers is 0.003 mg-min/m³ over eight hours (MMWR, 1988). For the general public, the limit established by the Army Surgeon General Working Group (MMWR, 1988) is 0.0001 mg-min/m³ over 72 hours (Watson and Griffin, 1992).⁹ The Environmental Protection Agency–recommended maximum levels of mustard in drinking water are 28 µg/liter for 5-liter daily intake and 9.3 µg/liter for 15-liter daily intake.

Unlike contact with lewisite, phosgene oxime, and riot-control agents, contact with mustards produces no immediate signs or symptoms. The subsections below review the delayed effects by organ. It should be kept in mind throughout the following that there are substantial differences among persons in their responses to mustards. Racial differences in sensitivity to mustards exist; dark-skinned people are more resistant (Vedder, 1925; Haldane, 1925). Other studies show up to a 100-fold difference in sensitivity (Hassett, 1963). Glutathione, which is important in mustard detoxification, has circadian variations in cellular levels and may be depleted by oxidative stress, medications, smoking, and ethanol.

The following excerpt provides a compelling overall picture of clinical mustard injury as observed in World War I mustard casualties:

On exposure to the vapor or to a finely atomized spray of mustard, nothing is noticed at first except the faint though characteristic smell. After the lapse of several hours, usually four to six, the first symptoms appear. The systemic symptoms are intellectual dullness or stupidity, headache, oppression in the region of the stomach, nausea or vomiting, malaise and great languor and exhaustion. In many cases these symptoms may not be noticed, and the local symptoms first attract attention. The eyes begin to smart and water. There is a feeling of pressure or often of a foreign body, and photophobia, and when examined the conjunctiva is found to be reddened. The nose also runs with thin mucous as from a severe cold in the head, and sneezing is frequent. The throat feels dry and burning, the voice becomes hoarse, and a dry harsh cough develops. Inflammation of the skin now shows itself as a dusky red erythema of the face and neck which look as though they had been sunburned, but are

⁹There are considerable variations in the data, which reflect differences in experimental design, extrapolations from animal studies, temperature, and individual differences. Increased ambient temperature and sweating can increase agent effects. Eye and respiratory systems have similar sensitivities, but eye effects generally have less latency (Somani, 1992, p. 54). The reverse cannot explain all the variances.

almost painless. The inner surfaces of the thighs, the genitals, the buttocks, the armpits, and other covered portions of the body are similarly affected. Mustard affects more severely those parts of the body where the skin is tender and well supplied with sweat glands. Itching and burning of the skin may be spontaneous, or first noticed as the result of washing. Even these mild symptoms may be sufficiently irritating to cause sleeplessness. At the end of 24 hours, a typical appearance is presented. The conjunctivitis has steadily increased in intensity, the vessels are deeply injected, and one of the main items of distress is caused by the pain in the eyes which may be very intense. The patient lies virtually blinded, with tears oozing from between bulging edematous eyelids, over his reddened and slightly blistered face, while there is a constant nasal discharge, and continuous harsh, hoarse coughing. Frontal headache is often associated with pain in the eyes and photophobia and blepharospasm is always marked. During the second day the burned areas of the skin generally develop into vesicles, and the scrotum and penis and other badly burned areas become swollen, edematous and painful to the touch. Bronchitis now sets in with abundant expectoration of mucus, in which there may later be found large actual sloughs from the inflamed tracheal lining. The temperature, pulse rate and respiration rate are all increased. (Vedder, 1925.)

These symptoms increase in intensity for several days if the case has been severely burned. On the other hand cases that have been only slightly poisoned may never proceed to the blister stage. Note that more recent literature often overlooks the mental and performance effects.

Eyes. The eyes were involved in some 85 percent of U.S. World War I mustard casualties (Gilchrist, 1928). One would have expected widespread “outbreaks” of conjunctivitis had there been extensive low-level exposures in the Gulf. Inflammation is one of the earliest symptoms of mustard exposure, varying from mild conjunctivitis, with lachrymation resembling that from a foreign body in the eye, and photophobia up to very severe injury. A severe keratitis with clouding and edema of the cornea is common, and there may be corneal ulceration (although this is rare) and superficial erosion. Loss of eye contents is rare (where corneal damage is so severe that it ruptures and vitreous contents leak out) (Vedder, 1925; McNamara et al., 1975). Subconjunctival hemorrhages have been reported in Iranian patients (Momeni and Aminjavaheri, 1994). As mentioned above, these symptoms manifest hours after initial exposure, but symptoms evolved more quickly following subsequent exposures (Otto, 1946). In uncomplicated cases, swelling and photophobia decrease after several days, and corneal clouding clears after several weeks. Blindness rarely results (Vedder, 1925). A delayed keratopathy with corneal erosions has been described 8 to 40 years after World War I acute exposures (Dacre and Goldman, 1996), but this effect appears to have been limited to persons with severe initial injuries involving cornea and conjunctivae (Sidell, Takafuji, and Franz, 1997, pp. 210–211).

Lohs (1975) describes chronic conjunctivitis and other delayed eye effects in World War II munitions plant workers. Dacre and Goldman (1996) reviewed Huntsville Arsenal reports of chronic conjunctivitis in mustard workers, whose symptoms cleared with short absences from work. Workers at Edgewood Arsenal were found to have decreased corneal sensitivity.

Respiratory. Respiratory injuries were the main cause of death in 75 percent of the 6,980 U.S. World War I mustard casualties analyzed (Gilchrist, 1928). Respiratory symptoms are expected for persons not wearing protective masks. Early symptoms (and symptoms from mild exposures that do not progress) include sneezing, nasal and throat irritation, and a loss of taste and smell within 12 hours (Vedder, 1925; Dacre and Goldman, 1996; Wachtel, 1941). The loss of taste and smell might be useful in retrospectively reviewing Gulf-associated medical records for evidence of mustard exposure.

More severe exposures produce laryngitis, aphonia, and incapacitating bronchitis, with severe constant coughing that worsens at night. A secondary pneumonia may occur within 36 to 48 hours. Difficulty swallowing begins on day 2 or 3 and lasts four to six days, and there may be a burning sensation in the pharynx and chest lasting several weeks. There is thick mucus and diphtheric-type pseudomembrane formation in the trachea and bronchi, with dyspnea and hypoxia in severe cases. Fever is common (Vedder, 1925; Wachtel, 1941; Dacre and Goldman, 1996).

Very severe exposures have the most complications, with bronchopneumonia due to *Staphylococcus*, *Streptococcus*, and *Pseudomonas*. X-rays show cellular infiltration and hypoxia and are consistent with adult respiratory-distress syndrome. Lung abscesses and tuberculosis activation have been reported. Persistent bronchiectasis also occurs (Vedder, 1925; Somani, 1992, pp. 55–57; Pauser et al., 1984; Sohrabpour, 1984; Colardyn and De Bersaques, 1984). Shedding of columnar cells has been seen in experimental animals and humans, along with disorganization of cells and atrophy of the tracheal and bronchial epithelium (Dacre and Goldman, 1996; Calvet et al., 1994).

Exposed munitions workers experienced a number of respiratory problems from their more sustained exposures, including chronic bronchitis, emphysema, and some bronchiectasis, and many were placed on disability (Dacre and Goldman, 1996). The high prevalence of chronic bronchitis and heavy smoking complicated the evaluation of chronic bronchitis, emphysema, asthma, and cancer following World War I exposures (Pechura and Rall, 1993). Epidemiologic studies in the UK and the United States did not find compelling evidence of a role for mustards in chronic pulmonary disease after acute World War I exposures (Dacre and Goldman 1996). Studies of Japanese munitions workers definitely show increased laryngeal and lung cancer among those exposed to

mustards (Tokuoka et al., 1986; Yamakido et al., 1996). Late long-term obstructive and restrictive disease is expected from mustards, as when the pulmonary fibrosis complicates the use of other alkylating drugs (Rall and Pechura, 1993). There is some controversy on these matters, especially on the long-term hazards of exposure without sign of acute injury (Rall and Pechura, 1993; Bullman and Kang, 1994).

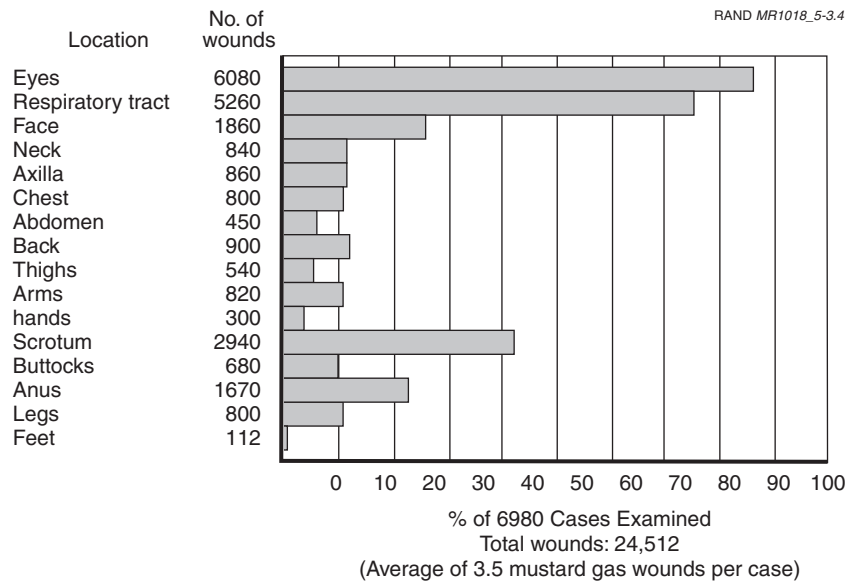
Skin. Although mustard is classed as a skin-damaging agent, the skin effects are neither the most common nor the most serious, but they can still be formidable. Also, the skin can be an important absorption pathway for the agent to produce system toxicity. Because they are lipophilic, the mustards readily penetrate the skin. Liquid or saturated vapor is absorbed at 1 to 4 $\mu\text{g}/\text{cm}^2/\text{min}$, indicating the importance of the total area exposed in determining toxicity. Labeled mustard penetrates the skin in 10 minutes (with 12 percent fixing in the skin, and 88 percent going into the circulation) (Papirmeister, 1991; Dacre and Goldman, 1996). Mustard vapor is absorbed more readily from the skin and lungs than are mustard aerosols. A concentration of mustard vapor as low as 1 mg/m^3 of air over the course of a day impairs the military efficiency of exposed troops (Wachtel, 1941).

A 10- μg droplet of mustard on the skin is sufficient to cause vesication. Of this, about 80 percent evaporates and about 10 percent enters the circulation, leaving only about 1 μg to produce the vesicle. The amount of mustard in a teaspoon, about 7 g, spread over 25 percent of body surface area is sufficient to cause death (Sidell, Takafuji, and Franz, 1997, p. 201).

Mustard does not produce skin injuries uniformly. The face, scrotum, and anal regions are frequently involved, while the hands are often spared. Figure 3.4 shows the anatomic frequency of involvement for nearly 7,000 World War I U.S. casualties. Data from Iran are similar (Momeni et al., 1992; Momeni and Aminjavaheri, 1994).

Warm, moist skin is more vulnerable to mustard injury, as the high prevalence of scrotal, anal, and axillary injuries indicates, so mustards are a greater threat during warm weather (Gilchrist, 1928). World War II studies in tropical areas showed increased vulnerability and delays in onset of 7 to 12 days (Dacre and Goldman, 1996).

Mild cases (estimated exposure 1 mg/m^3 for perhaps one hour) may show only erythema resembling a sunburn. Many mustard skin lesions result in hyperpigmentation, but that is not commonly mentioned for the mildest cases (Vedder, 1925; Requena et al., 1988; Helm and Weger, 1980). Groin erythema might further suggest possible low-level mustard exposure. There is a report of Stevens-Johnson syndrome with bullae and mucosal lesions following clinical use of nitrogen mustard (Newman et al., 1997).



SOURCE: Reprinted with permission from Vedder (1925).

Figure 3.4—Anatomical Distribution of World War I Mustard Injuries

Lesion resolution is prolonged. Papirmeister et al. (1991) give 22 to 29 days, collated from multiple experimental sources; most World War I casualties were hospitalized for 65 days (Smith and Dunn, 1991). These lesions resemble a medical condition called toxic epidermal necrolysis that has a 20-percent mortality rate. Secondary skin infections are problematic. The most severe cases may have marked fluid losses, hypovolemia, renal failure, and difficulty in retaining body heat. Large mustard injuries are associated with systemic illness, catabolism, poor appetite, depression, and secondary infections (Requena et al., 1988; Vedder, 1925).¹⁰

Resolving lesions are strikingly hyperpigmented (Requena et al., 1988). Intense burning during recovery, which is unresponsive to opioids but responsive to carbamazepine, has been described (Newman-Taylor and Morris, 1991). There is little scarring from these lesions, perhaps since the basal cell layer of the skin is the main location of injury, and there is little deep injury. Histologically, basophils are prominent, and serum enters the lesion carrying mediators and modulators of tissue injury (Dannenberg et al., 1985). Biopsies of human casualties at the erythema stage showed inter- and intracellular edema and

¹⁰Despite more significant systemic injury, mustard cases do not seem to have a higher incidence of mortality than cases of toxic epidermal necrolysis.

nuclear pyknosis, edema of the upper dermis and lymphocyte infiltration of the dermis. Later biopsies of bullous lesions showed perivascular infiltration by neutrophils and lymphocytes, with leukocytic infiltration of the dermis (Momeni et al., 1992).

Momeni et al. (1992) found 92 percent of 525 Iranian mustard casualties had skin lesions; 79 percent had erythema; 55 percent bullae; and 20 percent had pigmentation. Of note were findings of urticaria in 5 percent and purpura in 1.2 percent—conditions that had not previously been described in mustard cases.

Exposed German and Japanese mustard workers have multiple skin tumors (e.g., basal cell carcinoma, Bowen's carcinoma, and squamous cell carcinoma). World War I veterans did not apparently experience an increased prevalence of skin cancer; however, the U.S. Department of Veterans Affairs recognizes skin cancers arising from mustard application in its veterans as service related (Pechura and Rall, 1993).

Nervous System. Nervous system toxicity is evident in animals given high doses of H, especially intravenously, with a resulting cholinergic picture of hypersalivation, hypotension, bradycardia, and marked skeletal muscle weakness that begins superiorly and descends (OSRD, 1946; Krustanov, 1962; Dacre and Goldman, 1996). Atropine has some protective effects in animal models (Vojvodic et al., 1985). Krustanov (1962) showed that sublethal skin doses of mustard in rabbits sharply lower serum cholinesterase. Dacre and Goldman (1996) summarized a fatal human exposure to ingested mustard (suicide) with a similar clinical picture; pathological changes occurred in the brain, spinal cord, sympathetic ganglia, cerebellum, and olivary nuclei.

Neuromuscular. Neurological effects are subtly present at all levels of exposure but are primarily recognized with massive percutaneous or systemic poisoning. Symptoms include nausea, vomiting, nystagmus, reflex disturbances, decreased motor activity, apathy, disturbed consciousness, anxiety, excitement, insomnia, and depression and can proceed to seizures, coma, and death (Rebentisch and Dinkloh 1980; Momeni et al., 1992). Chronically exposed workers have impaired concentration, altered autonomic function, depression, and decreased vitality and libido and are hypersensitive to stimuli (Lohs, 1975).

In light of concern about neurological impairments in Gulf veterans, it is notable that Vedder (1925) repeatedly commented on lethargy and dulled thinking in milder mustard cases; in severe patients, he observed that “the picture is one of a serious disturbance of the central nervous system.” Overall, the picture resembles cholinergic overactivity, and mustards can impair AChE, although the significance of this is uncertain. To date, the neurological mechanisms of mustard injury have received little attention. No data emerged from

the literature that suggest that subtle neurological effects occur in persons who did not manifest more definite eye, respiratory, or skin injury.

The occurrence of post-traumatic stress disorder (PTSD) in World War II veterans involved in mustard experiments is somewhat surprising (Schnurr et al., 1996). However, in a November 1997 address to the Association of Military Surgeons, Dr. Horvath of the VA reported a very high prevalence of PTSD in veterans so exposed. Cholinergic mechanisms are involved in memory, and it is possible that the agent itself is contributing to this disorder. Although the anticholinesterase-exposed experimental subjects the NAS-NRC Committee on Toxicology (NAS, 1985) followed up on did not have indications of increased mental disorders, the stress of mustard exposures may have been greater, with obvious skin injuries and in some cases very unpleasant scrotal injuries (NAS, 1997). Subjects exposed to other agents have not reported PTSD (NAS, 1985).

Little attention has been paid to the muscle effects of mustards. Humans and animals exposed to high levels develop weakness, seizures, tremors, hypothermia, and increased creatine phosphokinase (Dacre and Goldman, 1996).

Cardiovascular. Intoxicated Bari-disaster patients manifested gradual shock and cardiovascular collapse that was unresponsive to fluid replacement (Infield, 1971; Dacre and Goldman, 1996). Circulatory collapse in some Iranian cases has been reported. Patients with large skin burns have hypovolemia, hemoconcentration, initial bradycardia with later tachycardia, and peripheral edema.

Hematologic and Lymphatic. Hematological effects include, at higher doses, bone-marrow depression, marked leukopenia, thrombocytopenia, and anemia. With milder exposures, white cell counts initially rise and then fall. The systemic effects of mustard include injury of immune cells in the skin and lymphatic system, with impaired resistance to infection and secondary *Staphylococcus*, *Streptococcus*, and *Pseudomonas* infections (Momeni et al., 1992). Casualties have low white counts similar to those of chemotherapy patients (Pauser et al., 1984).

Gastrointestinal. Intoxication is rapid and severe by this route. Mustard ingestion produces nausea, vomiting, abdominal pain, diarrhea, and later gastrointestinal bleeding with intestinal necrosis (Vedder, 1925). During World War I, constipation was a more common problem. The prevalence of gastrointestinal bleeding in Iranian casualties was low (10 percent) (Momeni et al., 1992). Systemic signs and symptoms with nausea and vomiting are common (as they are in radiation injuries), possibly representing an effect on the central nervous system rather than on the gastrointestinal tract, with loss of appetite, weakness, lethargy, and apathy.

Immune System. Mustards are immunogenic, perhaps by acting as haptens with proteins to which they bind. Persons with prior mustard exposure develop signs and symptoms at lower exposure levels than those with initial exposure. Contact sensitization to nitrogen mustards with urticaria and anaphylactic reactions is known (Daughters et al., 1973; Grunnet, 1976; Sanchez-Yus and Suarez, 1977).

Other Organ Systems. Mustards do not appear to have serious direct renal effects, although acute tubular necrosis can follow shock and hypotension. In experimental animals, low levels of mustard produce adrenal hypertrophy (Dacre and Goldman, 1996). Patients with substantial mustard injuries have changes in levels of thyroid hormones, thyroid stimulating hormone, cortisol, and adrenocorticotrophic hormone (ACTH) that are similar to those of burn victims, but these patients show a steady fall in cortisol levels despite high ACTH levels (Azizi et al., 1993).

Reproductive and Teratogenic Effects. Mustards inhibit spermatozoa production in animals for about four weeks (Dacre and Goldman, 1996). There do not appear to be similar effects on the ovary. Pregnant rats subjected to low levels of mustard did not show an increase of fetal mortality (McNamara et al., 1975). (See also the Iranian reports discussed in the next subsection.)

Chronic and Late Systemic and Miscellaneous Effects. Mustard workers (Lohs, 1975; Yamakido, 1996; Rall and Pechura, 1993; Dacre and Goldman, 1996) are in poorer health than their peers, with increased depression, chronic bronchitis, nervousness, infection, and autonomic disorders. Skin lesions can recur at sites of prior injury. They appear to have more eye difficulties and a higher prevalence of skin and respiratory tract cancer. It seems well established that mustards are mutagens and carcinogens (Brookes, 1990; U.S. Department of Health and Human Services, 1992).

Late effects from acute exposure have been published, mostly from the Iranian experience, although the analyses sometimes lack detailed rigor. These include:

1. cleft lip and palate (of 79 such defects per 21,000 live births, 30 were associated with mustard exposure) (Taher, 1992)¹¹
2. lung and skin problems, decreased libido (Pour-Jafari and Moushtaghi, 1992)
3. change in the ratio of male to female births (Pour-Jafari, 1994)
4. increased congenital malformations (258 in mustard-exposed versus 33 in controls per 1,000) (Pour-Jafari, 1994)¹²

¹¹Taher did not report on the total number of mothers exposed to mustards.

¹²But the contribution of other nutritional and environmental factors could not be excluded.

5. cough, fatigue and persistent headaches (Deneauve-Lockhart et al., 1992)¹³
6. decreased health perceptions and increased PTSD among U.S. men who had participated in mustard tests (Schnurr et al., 1996).

What to Look for in the Gulf Context

The Iraqis had considerable amounts of mustard, but there is only one probable case of mustard injury among U.S. troops. It is hard to know what to make of later press reports of an interview with that soldier who reported memory and cognitive problems. Such persisting problems were not described after World War I or reported by Iranians. It should be noted that mustards can affect the central nervous system in poorly understood ways. Although mustard effects should be included in considering the cause of the soldier's memory and cognitive problems, it is an anomalous event in the history of mustard exposures, and many other causes also need consideration (e.g., stress response), and there also may be possible medical reasons for memory loss.

Theoretically some mild mustard vapor exposures could be overlooked, because their symptoms—eye irritation, runny nose, sore throat, cough, malaise, and sunburn—like erythema—could be diagnosed as more-common disorders. As for other agents whose lower-dose effects can be misinterpreted, it is hard to visualize a situation in which a low-dose exposure of many persons and of such uniformity could occur that no definite typical clinical signs would develop. The soldier with probable mustard injury was rapidly and effectively identified as a possible mustard case. This review does not provide guidance about a role of mustard in complex interactions with other chemicals and drugs, except for speculative comments about cholinergic effects of mustards enhancing the effects of other cholinergic agents such as cholinesterase inhibitors (e.g., pyridostigmine bromide (PB), organophosphate pesticides, or nerve agents).¹⁴ Other stresses, such as smoking or ethanol, may lower glutathione levels and enhance the effects of mustards.

Summary

Exposure to mustard has not been known to result in symptoms that correspond to those seen in Gulf War veterans. The protracted symptoms of the one

¹³This is an isolated report of a 39-year-old French mechanical-shovel operator who exposed some mustard gas cylinders, which apparently were leaking. He developed eye irritation and laryngeal irritation, followed by nausea and dizziness several hours after exposure to the cylinders. The next day, he developed a fever and vesicles on his fingers and trunk. Two months later, he still had the complaints above.

¹⁴Chapter Five mentions animal research showing increased toxicity from combinations of nerve agents and mustards in Bulgarian research (Krustanov, 1962), while Vojvodic et al. (1985) has shown some protection of mustard-exposed animals by atropine.

probable casualty from mustard are atypical, unexpected, and not understood. Behavioral, cognitive, and performance consequences of low-level mustard exposures have not been comprehensively studied. At high and sustained doses, mustards produce chronic and serious delayed effects, but these effects are not expected from brief, low-level exposures. Mustards are mutagens and carcinogens, but the risk from brief lower exposures is apparently small. It may be possible to test archived tissues from the Gulf War to detect mustard that has interacted with DNA. The tests, although fairly well established, are not yet routine, and consultation with AFIP is advisable if they may seem useful for analyzing hypotheses about illnesses in Gulf War veterans. The loss of taste and smell characteristic of low-level mustard exposure might help differentiate mustard exposures from nonspecific respiratory infections and irritation.

Hypothesis and Analysis

Some mustard effects seem to be cholinergic, perhaps as a result of inhibiting AChE, and might increase the effects of other cholinergic chemicals in the environment, e.g., PB, organophosphate pesticides, or nerve agents. The previously noted wide variation in individual responses to mustards should be kept in mind. Although the finding of impaired memory (in one soldier) is unexpected, one cannot totally exclude mustard from contributing to cognitive problems. However, other veterans of the Gulf War with no evident mustard exposure have similar symptoms.

The high prevalence and long persistence of PTSD in World War II veterans exposed in studies (generally small, localized exposures with injuries that were not massive) remains an enigma. The simplest hypothesis is that the tests were extremely stressful (more so than in the experience of the nerve agent volunteers). Some properties of mustards might affect brain function. It has not been determined whether mustards (as is the case for several cholinergic agents) induce the expression of proto-oncogene (transcription factors) c-fos in the brain (Kaufer et al., 1998).