

Hazards of Chemical Weapons Release during War: New Perspectives

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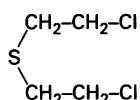
The two major threat classes of chemical weapons are mustard gas and the nerve agents, and this has not changed in over 50 years. Both types are commonly called gases, but they are actually liquids that are not remarkably volatile. These agents were designed specifically to harm people by any route of exposure and to be effective at low doses. Mustard gas was used in World War I, and the nerve agents were developed shortly before, during, and after World War II. Our perception of the potency of chemical weapons has changed, as well as our concern over potential effects of prolonged exposures to low doses and potential target populations that include women and children. Many of the toxicologic studies and human toxicity estimates for both mustard and nerve agents were designed for the purpose of quickly developing maximal casualties in the least sensitive male soldier. The "toxicity" of the chemical weapons has not changed, but our perception of "toxicity" has. **Key words:** chemical weapons, health effects, mustard gas, nerve gas, potency, toxicity. *Environ Health Perspect* 107:985-990 (1999). [Online 5 November 1999] <http://ehpnet1.niehs.nih.gov/docs/1999/107p985-990reutter/abstract.html>

The two major classes of chemical weapons are mustard gas and the nerve gases. Although both types are commonly called gases, they are actually rather viscous liquids that are not remarkably volatile. What is remarkable is that these agents were designed to harm people by any route of exposure and to be effective at low doses. It is also noteworthy that these major agent classes have not changed in over 50 years (1,2).

What has changed recently is our perception of the potency of the chemical agents (3), the inclusion of more women in the military, and the likelihood that targets may include civilians (4). We have also become concerned with the nonlethal, persistent, and delayed effects that may be produced (5-22). These issues are put into better perspective with some background knowledge of the effects of chemical weapons on humans, particularly via routes of exposure likely to be encountered following wartime release.

Mustard

Mustard gas, bis-(2-chloroethyl) sulfide (Chemical Abstract Service No. 505-60-2), is also known as mustard, S-mustard, sulfur mustard, HS, HD, H, Kampfstoffe, Lost, S-Lost, Schwefel-Lost, Y, Yellow Cross, and Yperite. At 25°C, the vapor pressure, liquid density, and volatility of mustard are 0.11 mmHg, 1.27 g/mL, and 920 mg/m³, respectively.



Although it is lethal in high doses and affects multiple organ systems, it is classed as a vesicant (blistering) agent (23,24).

Mustard was first synthesized in the early or middle 1800s, and its vesicant properties were understood at that time (25). Since then, it has been recognized as a radiomimetic (5) and a human carcinogen (24,26). It may also be teratogenic and mutagenic (27,28). Mustard is an alkylating agent, and once absorbed, its toxic effects result from chemical reactions with cellular constituents. These biochemical reactions cause inhibition of mitosis, nicotinamide adenine dinucleotide (NAD) depletion, decreased tissue respiration, and ultimately, cell death (23,24).

The first wartime use of mustard was by the Germans against the British at Ypres, Belgium, on 12 July 1917. Its physicochemical properties made it the chemical agent most widely used during World War I; mustard accounted for approximately 400,000 casualties—almost 77% of all the gas casualties (29). However, the death rate from mustard exposure was only about 2% (1,30-32).

Many of the toxicologic properties of mustard were not appreciated until after World War I. Approximately 95% of the men gassed with mustard had respiratory involvement. Eye lesions were even more common (33), and many soldiers were temporarily blinded (34). It also became apparent that a one-time exposure to a relatively high concentration of mustard could result in chronic or recurring effects (6-10,35). Respiratory problems were most frequently observed. However, skin and eye lesions that had apparently healed recurred spontaneously decades later (36,37). In addition, soldiers who had been gassed with mustard seemed to develop respiratory cancers more frequently than expected (9-11).

Despite the Geneva Convention of 1925, which prohibited the use of chemical weapons, mustard production continued,

and many countries generated large stockpiles. During World War II, there were numerous instances of occupational exposures at various production facilities throughout the world. Some of these exposures underscored the insidious nature of mustard gas. Employees did not realize that they had been exposed until symptoms developed the next day (38). Occupational experiences also indicated that chronic disability could result from mildly symptomatic exposure to relatively low concentrations for periods as brief as a few weeks (39-41). Given that mustard is relatively persistent, such observations are significant from a wartime perspective in that people exposed to prolonged off-gassing of mustard-contaminated material or terrain could develop chronic respiratory problems. Occupational exposures have also underscored the carcinogenic and mutagenic potential of mustard in humans (40-50).

Although it smells like garlic or mustard, disabling vapor concentrations may have so little odor that one is not aware of the danger until hours after exposure, when signs and symptoms begin to appear (24,25,51). Mustard does not cause pain upon contact, and there is a latent period before effects begin to occur.

This aspect of mustard is graphically underscored by the incident at Bari Harbor, Italy, in 1944. Although mustard was not used offensively, a number of casualties occurred when an Allied ship loaded with mustard-filled munitions was sunk in a German bombing. The destroyer *Bisterra* was in the harbor when the bombing occurred, and it participated in the rescue work. It is unknown whether the crewmembers were directly, but unwittingly, exposed to a mustard cloud or if they were exposed by the off-gassing of mustard-contaminated individuals who had been rescued from the harbor. The following is quoted directly from Alexander (52,53).

After picking up about thirty casualties, the harbor was ordered cleared and the *Bisterra* put to sea for Taranto. Four to six hours out of Bari, eye

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symptoms began to develop in the ship's officers and most of the crew. The commanding officer ordered immediate irrigation of everyone's eyes with an eye wash, but the symptoms continued to increase in severity. It was only with great difficulty that the ship was brought into Taranto harbor eighteen hours later, as the staff and crew were practically blinded by their acute eye lesions. These eyes cleared up rapidly and completely, but they did require hospitalization.

Following World War II, approximately 52,000 tons of mustard were dumped into the Baltic Sea; many fishermen have been exposed when they accidentally hauled up mustard-filled munitions and containers. As recently as 1984, 23 Baltic fishermen were exposed to mustard when they netted some mustard-filled shells that had been dumped into the ocean (23,54). Several of these fishermen were reported to have a significant increase in sister chromatid exchanges (SCEs) (55). SCEs are the result of breaking and rejoining of chromosomes and can be caused by alkylation of DNA.

Since World War I, mustard has been allegedly used by the following: Great Britain in the Middle East; the French in Morocco; Italy against Ethiopia in 1936; Japan against China in 1937; Poland against Germany in 1939; the Russians in Central Asia; Egypt against Yemen from 1963 to 1967; Iraq against Iran during the Iran-Iraq War, and Iraq against the Kurds (1,12,23,24,30). The findings in mustard-exposed Iranian soldiers are similar to those reported during World War I: eye and skin lesions, with more severe cases having respiratory and gastrointestinal problems (56-58).

Mustard is fat soluble and is readily absorbed through exposed tissues. The effects of mustard intoxication can be local, systemic, or both, depending on the route, extent, and duration of exposure, and may include one or more target organs. The systemic effects include bone-marrow inhibition with consequent reduction in the number of white cells and damage to the gastrointestinal tract. Local effects occur at much lower dosages than systemic effects, and exposure to airborne concentrations of mustard is unlikely to produce systemic effects in the absence of severe local effects on the eyes and respiratory tract (24).

There is a latent period of up to 24 hr or more between exposure and the onset of effects. Onset time is a function of dosage: higher dosages tend to produce more severe effects with shorter latent periods (59). Full-blown effects may not be manifest for several days (51). The latency period for eye injury is shorter than that for injury caused by equivalent dosages elsewhere on the body (24).

Moderate ocular effects can be produced without knowledge of exposure. Low

concentrations of vapor produce lachrymation and conjunctival injection. The presenting symptom is often a feeling of grittiness or the sensation that something is in the eyes. Higher concentrations produce corneal damage, photophobia, and blepharospasm. Any liquid mustard splashed into the eye is likely to result in blindness (60). Even in the absence of permanent ocular lesions, mustard vapor exposure produces temporary blindness, and ocular effects are those most likely to incapacitate the soldier.

By acute inhalation, mustard can produce sneezing, rhinorrhea, nosebleed, pharyngitis, hoarseness, coughing, bronchitis, tracheitis, tracheobronchitis, tachypnea, and pseudomembrane formation with subsequent pneumonia (24). Mild exposure damages the laryngeal and tracheobronchial mucosa. Moderate exposure causes hyperemia and necrosis of the mucous membranes of the respiratory tract. Severe exposure produces necrosis, exudation, and the formation of diphtherialike pseudomembranes. Recent human data indicate that the most commonly damaged parts of the respiratory system are the large airways, but in severe cases the lower airways and lung parenchyma are also affected (61). Any inhalation exposure produces lesions that predispose the individual to bronchopneumonia (62). Pneumonia may be accompanied by loss of appetite, diarrhea, fever, and apathy (63). Pneumonia was the proximal cause of death in the majority of mustard victims during World War I (24). Borak and Sidell (32) ascribed death to a combination of respiratory failure and bone marrow suppression. Similar findings were reported following the Iran-Iraq War (61).

If there is respiratory and ocular protection, the skin is then the target tissue for airborne mustard (64), and the skin is the primary target for liquid mustard. With relatively low doses, skin effects are limited to the exposed tissue. At higher doses, surrounding areas also become involved. The initial effect is often erythema, which can be likened to a sunburn, and is usually accompanied by pain and edema. Pruritis may precede or accompany the erythema or persist after it has subsided. Sloughing of the skin may occur following erythema (65). At higher doses vesication occurs and may be preceded or accompanied by nausea and vomiting and malaise. Vesication begins with the appearance of pinpoint vesicles that ultimately coalesce to form blisters (51). When blisters are present, care must be taken to prevent infection. Blisters may be large and painful and take months to heal. Once healed, the blistered skin may be hypopigmented or hyperpigmented (66). Very high doses of mustard may produce necrosis without vesication (67). The most sensitive areas of the body, those areas burned

at the lowest concentrations and most severely burned overall, are the axillae and genitals (25,58,66). Borak and Sidell (32) reported that nearly half of the American survivors of World War I mustard gas attacks had scrotal and perianal burns. The severity of effects (and presumably penetration and absorption) are strongly mediated by ambient temperature and humidity, increases of which exacerbate the human response by decreasing the effective dose (24).

The current medical countermeasures for acute mustard exposure are essentially those developed during World War I: symptomatic treatment combined with antibiotics to prevent secondary infections in damaged membranes (1,68). Although systemic effects are manifest only at higher doses, it has been estimated that 80-90% of mustard gas penetrating the skin rapidly passes into the circulation (69). If the exposed area is not decontaminated within a matter of 15 min or less, there is no way to prevent the subsequent effects (24,25,70-73).

Despite the extensive human database on mustard, many questions remain. The effects of battlefield exposure to mustard have been well described, but the doses that produce them are unknown and may have resulted from prolonged or repeated exposures. Controlled human studies on effective doses of mustard were carried out from approximately 1918 to the mid-1960s (12,34,65,74) and were typically conducted to determine the acute effects from relatively brief exposures. Some of the stated effective doses for these studies are somewhat conflicting (62,65). Given the analytical chemistry techniques and experimental methodology of those times, the level of precision associated with the reported vapor concentrations may have been less than optimal. Nonetheless, the larger body of available mustard data does not address many of the toxicologic questions being asked today.

Nerve Agents

The nerve gases or nerve agents are all fluorine- or cyanide-containing organophosphates (OPs) similar to insecticides. They are the most potent of the known chemical agents, are rapidly lethal, and are hazardous by any route of exposure. The nerve agent *O*-ethyl *S*-[2-(diisopropylamino)ethyl]-methylphosphonothioate (VX) is estimated to be 10^3 - 10^4 times more potent than the more potent commercially available OP insecticides (75). It is theoretically possible to disseminate the nerve gases in high enough vapor concentrations that one breath would be incapacitating or deadly (76).

Nerve agents are generally grouped into two classes: G and V (Table 1). G agents are derivatives of phosphoramidocyanidic or

methylphosphonofluoridic acid and include sarin (GB; isopropyl methylphosphono fluoride), tabun (GA; ethyl *N*-dimethylphosphoramidocyanidate), soman (GD; pinacolyl methylphosphonofluoridate), and GF (*o*-cyclohexyl-methyl-fluorophosphonate). V agents are derivatives of methylphosphonothioic acid (77). VX is the primary V-type agent. The relative potencies of the nerve agents are $VX > GD \approx GF > GB > GA$ (13,77). VX is the least volatile and the most potent. Although it is often perceived to be more of a percutaneous threat, VX poses a serious hazard if volatilized. By comparison, G agents do not present much of a contact hazard (78). Any liquid nerve agent splashed into the eyes is potentially lethal (30).

The first G agent, GA, was synthesized by the German scientist Gerhard Schrader (Leverkusen Laboratories, I.G., Farbenindustrie) in 1936. GB was synthesized about a year later (79). Other G agents were developed around the time of World War II, and the V-type agents were developed about 1950 (80). Although Germany had manufactured, munitionized, and stockpiled as much as 30,000 tons of GA and GB, they were not used during World War II. In fact, the Allies were not aware of these agents until several key German facilities were captured (30,80).

Our lack of knowledge of the nerve agents was graphically demonstrated in one of the initial experiences with captured GA. One- and 2-mm drops of GA were put onto test subjects to determine if it was a vesicant; the results were negative. A 1-mm drop was then placed into the eye of a rabbit to determine if the substance was designed to cause eye damage. The animal rapidly went into convulsions and died (30).

Nerve agents bind covalently to the enzyme acetylcholinesterase (AChE), irreversibly inhibiting it and causing accumulation of acetylcholine (ACh) at neuroeffector junctions in the peripheral and central nervous systems (14,79,81). Similarly, nerve agents inhibit the blood cholinesterases (ChEs), but these are not the targets of toxicity and are of unknown function (13). There is poor correlation between toxic signs

and symptoms, dose, and degree of blood ChE inhibition (13,79,82–85). Repeated small exposures can suppress virtually all the blood ChE activity while producing only negligible clinical effects (82,86). However, inhibition of blood ChE is often an excellent indicator of nerve agent (or other anti-ChE) exposure, and clinical signs—other than local effects—are unlikely to occur in the absence of inhibition of blood ChE.

The clinical signs and symptoms of nerve agent intoxication are caused by cholinergic overstimulation resulting from ACh accumulation (87,88). Severe intoxication is manifested by salivation, involuntary defecation and urination, sweating, lacrimation, bradycardia and hypotension, respiratory depression, collapse, convulsions, and death (13). The proximal cause of death is respiratory failure.

Vapor inhalation with concomitant ocular vapor exposure is the most effective and most likely route of administration, especially for the more volatile agents. The effects that occur at the lowest airborne vapor concentrations are miosis, rhinorrhea, and tight chest. These are direct local effects and can occur in the absence of any measurable inhibition of blood ChE (13,86).

Nerve agents also affect the nicotinic ACh receptor-ion channel complexes and bind to cardiac M2 receptors, but it is not clear that these effects occur at physiologic concentrations *in vivo*. Likewise, nerve agent-induced effects on gamma amino butyric acid (GABA)-ergic systems may be implicated in seizure activity at high doses (80).

Contrary to some OP insecticides, the nerve agents do not inhibit neurotoxic esterase at physiologic concentrations. OP-induced delayed neuropathy (OPIDN) is unlikely to occur except at doses greatly exceeding the median lethal dose (LD₅₀) (13,80,89–91).

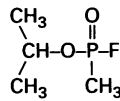
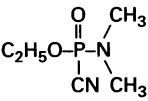
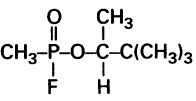
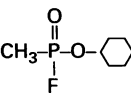
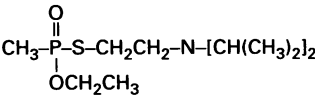
There have been allegations of military use of nerve agents by Iraq against Iranian soldiers and in combination with mustard against Kurdish civilians (1,80). These agents have been used by terrorists on civilian populations in Japan, and there was an accidental release of VX in a remote area of the United

States. No human injuries were reported, but 6,300 sheep were affected and 4,500 were directly killed by the agent or were required to be euthanized (92,93). There has been no large-scale military use of nerve agents.

Our knowledge of the human effects of nerve agents is based on human and animal studies, most of which were done to determine acute effects for brief exposures. Controlled human studies of very low doses were conducted from the 1940s to the 1980s (15,30). Accidental exposures of chemical agent workers and use of chemical weapons by terrorists have also contributed to the body of human data. Animal studies date from the 1940s to the present. In the older studies, many of the reported vapor concentrations are nominal, and analytical data, when available, were crude by today's standards. In some cases, review of the original data indicates that reported nominal vapor concentrations, when analytical data were also available, were 1.33–1.67% of the analytical concentrations. This means that the actual effective dosages may have been somewhat less than those reported (13). Some human exposures and other experiences with nerve agents will be briefly discussed to underscore the potency, severity, and rapidity of action of these chemicals.

As reported by Sidell (94), a worker in a nerve agent-contaminated area was wearing full protective gear while cleaning an area contaminated with GB. Upon later investigation it was discovered that the "voicemitter" diaphragm on his gas mask was cracked. He began to complain of increased oronasal secretions and difficulty breathing, and left the area. The worker quickly developed marked respiratory distress with copious secretions. Although he arrived at the emergency room within 5–10 min of his first symptoms, he was cyanotic and convulsing. His breathing was labored and he had muscular fasciculations, miosis, marked salivation, and rhinorrhea. He was treated with atropine and pralidoxime but required mechanical ventilation. Abnormalities in his electrocardiogram precipitated subsequent hospitalization elsewhere. Following recovery, the worker experienced a prolonged period of

Table 1. Physical and chemical properties of nerve agents.

Properties	Sarin (GB)	Tabun (GA)	Soman (GD)	GF	VX
Structural formula					
CAS no.	107-44-8	77-81-6	96-64-0	329-99-7	50782-69-9
Liquid density at 25°C	1.09 g/mL	1.08 g/mL	1.02 g/mL	1.13 g/mL	1.0083 g/mL
Volatility at 25°C	2.2×10^4 mg/m ³	610 mg/m ³	3900 mg/m ³	581 mg/m ³	10.5 mg/m ³
Vapor pressure at 25°C	2.9 mmHg	0.07 mmHg	0.40 mmHg	0.044 mmHg	0.0007 mmHg

Abbreviations: CAS, Chemical Abstract Service; GF, *o*-cyclohexyl-methylfluorophosphonate; VX, *O*-ethyl *S*-[2-(diisopropylamino)ethyl]methylphosphonothioate.

mental depression, possibly attributable to the nerve agent. Approximately 18 months after exposure, he died from a myocardial infarction. Autopsy confirmed severe coronary artery disease. It is possible that the initial abnormalities on the electrocardiogram may have resulted from a myocardial infarction and not from the direct effects of the GB on cardiac tissue (13).

In June of 1994, a terrorist group released GB into a civilian population in Matsumoto, Japan. The most severely affected survivor noted blurring of his vision after opening a window. He went to bed 2 hr later and was found unconscious the next day. Seven people were killed, and 600 were affected; 58 were admitted to hospitals (16,17).

On 20 March 1995, the same terrorist group released liquid GB in parcels in the Tokyo subway at rush hour. Twelve people were killed and over 5,000 required emergency medical evaluation (18). Most of the exposed individuals presented with miosis, and many had headaches. More than half experienced respiratory difficulties and nausea. Many others experienced eye pain, blurred vision, dim vision, rhinorrhea, and vomiting. About 17% were categorized as moderately toxic, a category that included all symptoms through convulsions as long as mechanical ventilation was not required. The average hospital stay for this group was 2.4 days. Less than 1% were severely affected, but all required mechanical ventilation and were hospitalized for more than a week (18). If the agent had been actively disseminated, the number and severity of casualties would have been significantly higher. People who were near the liquid-filled parcels or who were contaminated with liquid received the highest doses. Some fatalities were documented (16,18).

Early human studies with GA tested dosages of 0.7–30 mg/min/m³ (2- to 10-min exposures; some individuals had ocular or respiratory protection). Observed effects ranged from tight chest at the lowest dosages to miosis, frontal headache, retrobulbar pain, ocular erythema, rhinorrhea, nausea and vomiting, tight chest, blurred vision, sleep disturbances, lassitude, and visual changes, some of which persisted for over a week (13,30).

Some studies with GB have shown 100% miosis and tight chest at dosages as low as 0.6 mg/min/m³ (1-min exposure; analytical concentration). Higher dosages produced marked visual symptoms and frontal headache. Other human exposures to GB vapor indicate that dosages > 15 mg/min/m³ (1.5-min exposure) produce a marked fall in blood AChE, with concomitant pronounced symptoms of systemic nerve gas poisoning including generalized weakness, nausea and vomiting, and eye and respiratory effects. This dosage has

been suggested as the lower limit of physical incapacitation (13).

It is well documented that recovery from miosis can take days or weeks (79). Recovery of ChE activity can take months (87,95,96). It has also been reported that electroencephalogram and electromyogram abnormalities can persist for over a year and are sometimes not demonstrable without highly sophisticated techniques (15,19–22,79). This perspective was potentially corroborated by the Tokyo incident. Epileptiform electroencephalograms were observed in two individuals and persisted for 11 months in one; neither had clinical seizure activity (17). The significance of these effects is not well understood (22), and more data are needed before the determination can be made that these changes do not represent adverse effects (14,30,97). Psychiatric sequelae have also been reported after anti-ChE poisoning and may be more common after severe intoxication than currently thought (94). Morphologic brain damage has been observed in animals surviving prolonged seizures. Marrs et al. (30) consider it “probable that both histopathological changes and functional deficits” would be observed in humans surviving sublethal doses.

Safety considerations have impacted the body of data for most of the nerve agents, particularly GD and VX. [GD is refractory to oxime treatment (30) and VX is extremely potent.] Such considerations have also impacted experimental paradigms, and many human and animal studies have employed noninhalation routes of administration, despite the fact that vapor inhalation is usually the most probable route of exposure. Although the effects produced by the nerve agents are somewhat independent of the route of exposure, the order of their appearance and their clinical importance are very much a function of the route of exposure. Percutaneous exposure will not produce miosis unless the exposure is severe enough to produce systemic effects (80). When this is the case, the median effective dose (ED₅₀) for miosis is not significantly different from the LD₅₀; one may be prostrate, convulsing, and moribund before miosis occurs (98).

Clearly, the effects of nerve agent intoxication can be local, systemic, or both, depending on the dose and the route of exposure. However, it is difficult, if not impossible, to delineate doses that fall into a specific category of effect. The dose–response curves for the nerve agents are very steep. Given this and their potency, the transition from local to systemic effects can be quite abrupt. Doses producing severe effects are not significantly different from those that are lethal (13).

Following vapor inhalation, local effects include tracheobronchial constriction,

excessive secretions, and paralysis of the diaphragm and other respiratory muscles. Central effects include paralysis of the autonomic function in the brainstem. Respiratory failure can be central, peripheral, or a combination of the two (99,100). The predominant site of failure is a function of the route of exposure and the species. Vapor inhalation produces airway obstruction secondary to excessive secretions and bronchoconstriction, and peripheral neuromuscular weakness and respiratory paralysis are likely to predominate (13,79,101).

With systemic absorption, the effects of nerve agents on the central nervous system (CNS) include drowsiness, difficulty concentrating, emotional lability, sleep disturbances, excessive dreaming and nightmares, depression, lassitude, irritability, loss of libido, memory loss, and difficulty concentrating. Many of these can occur at very low doses. More severe effects include collapse, prostration, convulsions, respiratory failure, and death (13,20,87). Other systemic effects include nausea and vomiting, hypermotility of the lower bowel, and involuntary urination (87). Percutaneous effects are local effects and include localized sweating and muscular fasciculation in the immediate vicinity of agent contact.

Changes in Perspectives on the Hazards of Chemical Weapons

Recent reviews of the available toxicologic data for chemical weapons (3) have recommended downward revisions in some of the human toxicity estimates for military personnel for mustard and the nerve agents. It is important to understand why our perception of the potency of these chemicals has changed and to comprehend some of the factors that impact the effective doses of chemical agents.

Most of the available toxicologic data and concomitant human toxicity estimates were generated when the chemical weapons were being developed. The purpose of many studies was to determine which chemicals rapidly produced severe, acute effects at the lowest doses. Likewise, many of the human toxicity estimates were developed from the perspective of how quickly such effects were produced in the least sensitive, healthy, male soldier (3). Given that the time to effect is inversely proportional to the dose, the apparent time to effect was reduced by making the estimated doses larger than necessary to produce the specified end points. Even for mustard, the human estimates were intended to reduce the normal latency period of ≥ 1 day to a few hours for the development of full-blown effects.

Sex and body size were not a concern when the chemical weapons were being developed, and potential sex differences are not well characterized in the animal data.

Given the makeup of the military at the time, the subjects in the controlled human studies were fit, relatively young male soldiers, and the majority of the reported accidental exposures also involved men (30,83,102).

This has changed. Potential targets include women in military and civilian populations (4). There is also concern over sublethal effects produced by relatively low doses over relatively long exposure periods (12–18). There are few such data, particularly for appropriate exposure routes.

Based upon both sex and weight, differences have been anticipated in the sensitivity of women to chemical agents as compared to men (3). Studies have shown sex and hormonal effects on peripheral ChE (103). A recent review (13) concluded that such differences are likely, and they may be route- and agent-dependent; the most marked findings are via inhalation exposure. In the latter case, females were twice as sensitive as males to GB (13). When civilians become military targets, age, health, and sex factor into the sensitivity of the population. Diverse civilian populations will be more sensitive than a population of healthy adult workers or soldiers. Some studies have indicated as much as a 10-fold difference (104). Therefore, it should not be assumed that human toxicity estimates derived for male soldiers are applicable to female soldiers, and it should be assumed that a civilian population would be more sensitive than a military population.

Sublethal effects were not end points of concern when the nerve agents were being developed. The intent was to produce incapacitation or death very quickly after a relatively brief exposure to a rather high concentration. Similarly, with mustard gas the aim was to produce very severe effects as quickly as possible. Given this and the physical properties of the agents, toxicologic studies were conducted accordingly. Sublethal effects were typically not the toxicologic end points of animal studies, particularly for nerve agents. Further, some of the less severe effects in humans (nausea, vomiting, headaches, nightmares, visual degradation, involuntary urination, depression, amnesia, malaise) are difficult to discern in many laboratory species. Although the human exposures were done at sublethal levels, they do not encompass the spectrum between doses that produce very mild effects and those that are just sublethal, nor were they done from the perspective of effects produced by very low doses received over a period of hours or days (30). As a result, there are still many unknowns in the linearity of the dose-response curves of the agents over time. Haber's Law is not valid for the nerve agents, even for exposure durations ranging from 2–10 min, and there are few data available for longer exposures (3,13). For some agents it is

very clear that higher concentrations for a short exposure are more effective than lower concentrations for a longer exposure duration; the dosage in milligrams per minute per cubic meter increases as exposure time increases (13). For other agents the converse may be true. Similarly, few studies have been done with mustard to delineate this concentration–time relationship.

Summary

The two major threat classes of chemical weapons are mustard gas and the nerve agents. Mustard was used in World War I, and there is an extensive human database on it. The fact that mustard gas is a carcinogen and readily produces a variety of chronic or persistent effects was not fully appreciated until after the war and following extensive human occupational exposure prior to World War II. The nerve agents were developed shortly before, during, and after World War II. Nerve agents can be rapidly lethal, and the experimental human database is considerably more limited than that for mustard. Also, there has been no large-scale military use of nerve gas. It has, however, been used by terrorists on civilian populations. Nerve agents may produce histopathological changes in the CNS and electrophysiologic changes in the CNS and the peripheral nervous system. Many of the toxicologic studies and human toxicity estimates for both mustard and the nerve agents were generated for the purpose of developing chemical agents that would quickly produce maximal casualties in the least sensitive male soldier. Today our concern is the objective estimation of doses and effects for the typical soldier, both male and female. We must also consider the effects of chemical agents on civilian populations and the effects of prolonged exposures to relatively low doses (105). The questions being asked are different than those for which the historical data were generated. These materials have always been extremely potent and efficacious. Their toxicity has not changed, but our perception of it has.

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