ANNEX 1: CHEMICAL AGENTS

1. Introduction

The large-scale use of toxic chemicals as weapons first became possible during the First World War (1914–1918) thanks to the growth of the chemical industry. More than 110 000 tonnes were disseminated over the battlefields, the greater part on the western front. Initially, the chemicals were used, not to cause casualties in the sense of putting enemy combatants out of action, but rather to harass. Though the sensory irritants used were powerful enough to disable those who were exposed to them, they served mainly to drive enemy combatants out of the trenches or other cover that protected them from conventional fire, or to disrupt enemy artillery or supplies. About 10% of the total tonnage of chemical warfare agents used during the war were chemicals of this type, namely lacrimators (tear gases), sternutators and vomiting agents. However, use of more lethal chemicals soon followed the introduction of disabling chemicals. In all, chemical agents caused some 1.3 million casualties, including 90 000 deaths.

During the First World War, almost every known noxious chemical was screened for its potential as a weapon, and this process was repeated during the Second World War (1939–1945), when substantial stocks of chemical weapons were accumulated, although rarely used in military operations. Between the two world wars, a high proportion of all the new compounds that had been synthesized, or isolated from natural materials, were examined to determine their utility as lethal or disabling chemical weapons. After 1945, these systematic surveys continued, together with a search for novel agents based on advances in biochemistry, toxicology and pharmacology. The chemical industry, not surprisingly, was a major source of possible agents, since most of the new chemical warfare agents had initially been identified in research on pesticides and pharmaceuticals.

Few candidate chemical warfare agents satisfy the special requirements of their potential users, including acceptable production costs as well as appropriate physical, chemical and toxicological properties. Of the many hundreds of thousands of chemicals screened, only about 60 have either been used in chemical warfare or stockpiled for possible use as weapons. Two-thirds of them were used during the First World War, when battlefields also served as testing grounds. Fewer than a dozen chemicals were then found to be effective, but have since been supplemented or replaced by a similar number of more recently developed chemicals.

The properties of some of these chemicals are described below. They are grouped according to one of the classifications set out in Chapter 3 (see Table 3.1): (i) *lethal chemicals*, intended either to kill or to injure the enemy so severely as to necessitate evacuation and medical treatment; and (ii) *disabling chemicals*, used to incapacitate the enemy by causing a disability from which recovery may be possible without medical aid. Their properties are summarized in Table A1.1.

The chemicals included in Table A1.1 are not the only toxicants that can kill or injure on a large scale. Before the Chemical Weapons Convention was adopted, chemicals were selected as chemical warfare agents primarily because they had characteristics

that made them so aggressive that munitions disseminating them would be competitive with conventional weapons. Nowadays, less aggressive toxicants might be used, especially where accessibility or terrorizing potential rather than casualty cost-effectiveness dominates weapons choice. There are many commercial chemicals that, although less toxic than those described here, could cause great harm, as the release of methyl isocyanate in Bhopal, India, in 1984 bears witness. Information about the properties of such toxic industrial chemicals (TICs) is widely available, e.g. on pesticides. Some high-hazard TICs are shown in Table A1.2. When considering the threat from the deliberate release of chemicals, it is therefore appropriate to take account, not only of the chemical warfare agents set out in the Schedules of the Chemical Weapons Convention, but also of such TICs as may be present in hazardous quantities, their location and their transportation between industrial facilities.

Unless otherwise indicated, the information given in this Annex on each agent has been taken either from the First Edition of the present study or from the Hazardous Substances Data Bank, which is a toxicology file of the Toxicology Data Network (TOXNET®) of the United States National Library of Medicine.

Table A1.1. **Some properties of selected lethal and disabling chemicals**

CAS[a] Registry Number, class and properties	Common name							
	Sarin	**VX**	**Hydrogen cyanide**	**Phosgene**	**Chloropicrin**	**PFIB[b]**	**Mustard gas**	**Lewisite**
CAS Registry Number	107-44-8	50782-69-9	74-90-8	75-44-5	76-06-2	382-21-8	505-60-2	541-25-3
Class	Nerve gas	Nerve gas	Blood gas	Asphyxiant	Asphyxiant	Asphyxiant	Vesicant	Vesicant
Melting/freezing point (°C)	–56	–51	–14	–118	–64	–156	14	–17
Boiling point (°C)	147	298	26	8	112	-29	228	190
Volatility at 20 °C (mg/m^3)	16 100	12	873 000	6 370 000	165 000	Gas	625	3000
Relative vapour density	4.86	9.2	0.93	3.5	5.7	5.5	5.4	7.2
Solubility in water at 20 °C (%)	100	1–5	100	Reacts	0.2	Insoluble	0.1	Slightly
Airborne concentration perceptible to human beings (mg/m^3)	–	–	30 000	6	2	–	1.3	–
Airborne concentration intolerable to human beings (mg/m^3)	–	–	–	–	25	–		–
Lethality in rats: reported sc LD_{50} (mg per kg) [or reported inhal LCt_{50} ($mg.min/m^3$)]	0.12 [220]	0.015	1.1 (cat) [1550]	– [1880]	10 (cat)	– [1235]	1.5–5.0 [420]	1.0 [1500]
Estimated median effective airborne dosage for incapacitation of human beings ($mg.min/m^3$)	5	0.5	2000	1600	–	–	100	300
Estimated median lethal airborne dosage for human beings ($mg.min/m^3$)	70–100	50	1000–2000	5000	20 000	–	1000–1500	1200
Estimated median lethal percutaneous dosage for human beings (mg)	1700	6	7000	–	–	–	7000	2500

[a] CAS: Chemical Abstracts Service. [b] Perfluoroisobutene.

Sources: Vojvodić V, *Toksikologija bojnih otrova*. [*Toxicology of war gases*.] Belgrade, Vojnoizdavački Zavod, 1981; Marrs TC, Maynard RL, Sidell FR, *Chemical warfare agents: toxicology and treatment*. Chichester, Wiley, 1996; Hazardous Substances Data Base, available on CD ROM from Canadian Centre for Occupational Health and Safety, 250 Main Street East, Hamilton, Ontario, Canada L8N 1H6; Aaron HS, *Chemical warfare agents: a historical update from an American perspective*, US Army Biological and Defense Agency, report ERDEC-SP-004, April 1993; Klimmek R, Szinicz L, Weger N, *Chemische Gifte und Kampfstoffe: Wirkung und Therapie*. [*Chemical poisons and war agents: effect and therapy*.] Stuttgart, Hippokrates Verlag, 1983; Franke S, *Lehrbuch der Militärchemie* [*Textbook of military chemistry*], *Vol. 1*. Berlin, Militärverlag der Deutschen Demokratischen Republik, 1977.

Table A1.1 (continued). **Some properties of selected lethal and disabling chemicals**

CAS[a] registry number, class and properties	Common name					
	Lysergide	**BZ**	**Adamsite**	**CN**	**CS**	**CR**
CAS Registry Number	50-37-3	6581-06-2	578-94-9	532-27-4	2698-41-1	257-07-8
Class	Psychotropic	Psychotropic	Irritant	Irritant	Irritant	Irritant
Melting/freezing point (°C)	83	164	195	54–55	94–95	72
Boiling Point (°C)	Decomposes	320	410	245	310	335
Volatility at 20 °C (mg/m^3)	Negligible	0.5	0.02	105	0.35	0.63
Relative vapour density		11.7	9.6	5.3	6.5	6.7
Solubility in water at 20 °C (%)	Insoluble	Soluble	0.6	Insoluble	0.05	0.01
Airborne concentration perceptible to humans (mg/m^3)	–	–	0.1	0.3	0.05–0.1	0.003
Airborne concentration intolerable to humans (mg/m^3)	–	–	2–5	4.5	1–5	0.7
Lethality in rats: reported sc LD_{50} (mg per kg) [or reported inhal LCt_{50} ($mg/min.m^3$)]	16 (iv)	–	– [3700]	50 [3700]	>100 [32 500]	–
Estimated median effective airborne dosage for incapacitation of human beings ($mg/min.m^3$)	10-100	100–200	20–25	50	5–10	0.15
Estimated median lethal airborne dosage for human beings ($mg/min.m^3$)	–	200 000	15 000–30 000	8500–25 000	25 000–100 000	>100 000
Estimated median lethal percutaneous dosage for human beings (mg)	–	–	–	–	–	–

[a] CAS: Chemical Abstracts Service.

Table A1.2. **Some high-hazard toxic industrial chemicals**

Ammonia	Arsine	Boron trichloride
Boron trifluoride	Carbon disulfide	Chlorine
Diborane	Ethylene oxide	Fluorine
Formaldehyde	Hydrogen bromide	Hydrogen chloride
Hydrogen cyanide	Hydrogen fluoride	Hydrogen sulfide
Fuming nitric acid	Phosgene	Phosphorus trichloride
Sulfur dioxide	Sulfuric acid	Tungsten hexafluoride

Source: NATO International Task Force 25 (ITF-25), *Reconnaissance of industrial hazards*, as quoted in *Chemical and biological defense primer*, Washington, DC, Deputy Assistant to the US Secretary of Defense for Chemical and Biological Defense, October 2001, p. 11.

Note: ITF-25 did not rank industrial chemicals according to toxicity alone, but according to a hazard index reflecting such factors as the volume in which a chemical might be present in an area of concern, the inhalation toxicity of the chemical, and whether it existed in a state that could give rise to an inhalation hazard. Those listed here are from the high-hazard end of the ranking. Two (hydrogen cyanide and phosgene) are listed in part A of Schedule 3 of the Chemical Weapons Convention, signifying their past use as chemical-warfare agents. Another (phosphorus trichloride) is listed in part B of Schedule 3, indicating its past use as an agent precursor. Because the hazard index for a given chemical will vary from country to country, the ranking is not universal. For example, in countries where tungsten hexafluoride is present only in laboratories and in small quantities, its hazard index will be low.

2. Lethal chemicals

The lethal chemicals known to have been developed into chemical-warfare agents, and TICs too, may be divided into two groups: (i) tissue irritants; and (ii) systemic poisons. The first group contains the choking gases (lung irritants or asphyxiants) and the blister gases (vesicants), the second the blood and nerve gases.

Chlorine, an asphyxiant, was the first lethal chemical to be used in the First World War. In the spring of 1915, massive surprise attacks with the gas caused thousands of casualties, none of whom had any protection against such an airborne poison. Respirators used to protect troops were crude at first, but rapidly became more sophisticated. In parallel with these developments in the technology of defence were efforts to find agents more aggressive than chlorine. Widespread use of phosgene and diphosgene followed. Hydrogen cyanide was produced, but its physical properties (it is lighter than air) proved poorly suited to the munitions of relatively small payload capacity that were characteristic of most of the available delivery systems at that time. Another trend was the development of substances such as chloropicrin, the physical

and chemical properties of which enabled them to penetrate the respirators then available. The third and most significant development was that of agents such as mustard gas and the arsenical vesicants, e.g. lewisite, which damaged the skin and poisoned through skin penetration.

Among the many new chemicals reviewed for their chemical-warfare potential during the 1920s and 1930s were *bis*(trichloromethyl) oxalate, a congener of phosgene, and the tetrachlorodinitroethanes, congeners of chloropicrin. Other chemicals examined included disulfur decafluoride; various arsenical vesicants; nitrogen mustards and higher sulfur mustards; metallic carbonyls; cadmium, selenium and tellurium compounds; fluoroacetates; and carbamates. A few were found to offer some advantages over existing chemical warfare agents for particular purposes and were put into production. None, however, was thought superior to phosgene or mustard gas in general utility, and it was these two agents that formed the bulk of the chemical weapons stockpiled at the start of the Second World War, just as they had at the end of the First.

The most significant development in the lethal agents occurred at the time of the Second World War, when Germany manufactured tabun, the first of what became known as the G-agent series of nerve gases. A pilot plant for producing tabun was operating when war broke out in September 1939. At the war's end in 1945, some 12 000 tonnes of tabun had been produced, much of it filled into munitions. Tabun is both more toxic and faster acting than phosgene. Inhalation is a primary route of exposure, but casualties can also be caused if nerve agents penetrate the eye or skin, albeit at higher dosages.

Work continued on the G agents in several countries after the war. Sarin, first characterized in Germany in 1938, emerged as one of the more attractive nerve gases for military purposes. It went into production, when methods were developed that overcame the difficulties that had precluded its large-scale manufacture during the war. In the early 1950s, the first of what became known as the V agents was discovered in an agrochemical laboratory. Members of the series, such as VX and VR, are considerably more toxic than the G-agent nerve gases, especially if absorbed through bare skin.

During the Gulf War of 1981–1988, United Nations investigators collected evidence of the use of mustard gas and nerve agents. During the war, more than 100 000 Iranian military and civilian personnel received treatment for the acute effects of Iraqi chemical weapons (*1*), and 25 000 people were killed by them (*2*), a number that continues to increase. In addition, 13 years after the end of the war, 34 000 of those who had been acutely affected were still receiving treatment for long-term effects of the weapons (*1*). Evidence also exists of the widespread use of chemical-warfare agents against centres of population in Kurdish areas of Iraq in 1988. In particular, soil and other samples collected from the vicinity of exploded munitions were later analysed and found to contain traces of mustard gas and sarin. Iranian military personnel and Kurdish civilians have been treated in hospitals in Europe and the United States for mustard gas injuries. Health surveys within the Kurdish regions affected have, however, been limited, and the present health status of the population remains to be determined (*3*).

2.1 Lung irritants

2.1.1 *Phosgene*

Also known as carbonyl dichloride (CAS Registry Number 75-44-5), phosgene is a colourless gas at most ambient temperatures, but a fuming liquid below 8.2 °C. It is easily liquefied under pressure.

Sources
Phosgene does not occur naturally. First prepared in 1812, it is widely available in the chemical industry, where it is used as an intermediate in the manufacture of dyestuffs, pesticides, pharmaceuticals, polymers, resins and hardeners, among other products. Annual production in the United States is about 1 million tonnes, in Europe about 1.2 million.

Phosgene is also produced during the thermal decomposition or photo-oxidation of chlorinated solvents, and when polyvinyl chloride (PVC) is burned.

Exposure
Inhalation is the principal route. At high concentrations, skin and eye irritation occur. The lung is the main target organ, and damage to it following acute exposure to phosgene obeys Haber's Law, i.e. injury is the product of the concentration and duration of exposure. Haber's Law does not apply in chronic exposures.

Phosgene is variously described as smelling like decaying fruit, fresh-cut grass or mouldy hay. Trained workers can detect it at concentrations of 0.4 ppm. The odour threshold is generally about 1.5 ppm. Eyes, nose and throat become irritated at 3–4 ppm. Dosages damaging to the lung are 30 ppm.min or greater. Pulmonary oedema occurs at dosages exceeding 150 ppm.min (600 mg.min/m^3) (*4*).

Latency period and recovery time
Irritation of the eyes, nose and throat, together with chest tightness, occur rapidly at concentrations exceeding 3 ppm, followed by shortness of breath and a cough. If these are the only symptoms, they abate rapidly after exposure ceases. At dosages exceeding 30 ppm.min, the initial irritation and respiratory symptoms are followed by a second (possibly asymptomatic) phase, the duration of which is inversely proportional to the inhaled dose. After large doses, it may be 1–4 hours; after small doses, 24–48 hours. Pulmonary oedema, sometimes fatal, occurs in the third phase. If the patient survives, clinical and radiological oedema resolve within a few days. Antibiotics can be used if signs of infection develop. Residual bronchitis can last for several days. Blood gases and carbon monoxide diffusion normalize within a week. However, exertional dyspnoea and increased bronchial resistance may persist for several months (*5*).

Main clinical symptoms
Burning and watering of the eyes, a sore or scratchy throat, dry cough and chest tightness usually indicate exposure to concentrations exceeding 3 ppm. These symptoms are only a rough guide to the possibility of more severe lung injury.

Exposures to 2 ppm for 80 minutes will not cause any irritation but result in pulmonary oedema some 12–16 hours later (*6*).

Sense of smell is a poor guide to possible concentrations. At high concentrations, olfactory fatigue sets in, and subjects lose their sense of smell and their ability to assess the danger.

Erythema of the oral and pharyngeal mucous membranes is seen at higher concentrations.

Moist rales may be evident in lung fields and indicate the presence of pulmonary oedema. Lengthening of respiration occurs, indicating bronchiole luminal narrowing. Dyspnoea develops, and patients produce increasing amounts of sputum, which becomes frothy. Blood is viscous, and coagulates readily. Methaemoglobin concentrations increase and cyanosis and reduced arterial blood pressure follow, causing a marked increase in heart rate. The terminal clinical phase of lethal poisoning causes extreme distress with intolerable dyspnoea until respiration ceases. Phosgene intoxication always produces a metabolic acidosis and a compensatory hyperventilation. Arterial blood gases usually indicate hypoxaemia (*5*).

At very high concentrations (>200 ppm), phosgene passes the blood–air barrier, causing haemolysis in the pulmonary capillaries, congestion by red cell fragments and stoppage of capillary circulation. Death occurs within a few minutes from acute cor pulmonale (acute enlargement of the right ventricle). Contact with liquid phosgene may cause skin damage or blistering.

Most survivors of acute exposure have a good prognosis, but shortness of breath and reduced physical activity may persist in some for the remainder of their lives. Smoking appears to worsen the chances of recovery, and pre-existing lung disease, e.g. emphysema, will exacerbate the effects of phosgene exposure (*7*).

Long-term health implications
Evidence suggests that phosgene is unlikely to be mutagenic. Data on carcinogenicity are insufficient for an assessment.

Detection
A number of techniques are available to determine air concentrations, including passive dosimetry, manual and automated colorimetry, infrared spectroscopy and ultraviolet spectrophotometry. Paper tape monitors capable of detecting 5 $\mu g/m^3$ have been described. Other methods employ an absorbent and solvent (*4*).

Principles of medical management
Rapid triage in the following order should be carried out:

1. Severe respiratory distress.
2. Dyspnoea — at first with exertion, later at rest.
3. Cough, irritation of eyes and throat.
4. Irritation only.

Victims should be removed from the source of exposure and their clothing loosened. If they are in contact with liquid phosgene, contaminated clothing and footwear should be removed and the affected area gently warmed with lukewarm water.

Patients should be observed for up to 48 hours. If oedema develops, it will be apparent by this time. Warmth, rest and quiet are vital for all patients (*4*, *5*).

Prophylaxis/treatment
Affected skin and eyes should be flushed with running water for 15–20 minutes.

It is important to differentiate between early irritant symptoms and pulmonary oedema evident on chest X-ray. Irritation will precede oedema. However, oedema may sometimes develop in the absence of lung irritation.

Early oedema may be detected by chest X-ray before evident clinical signs appear by using 50–80 kV; at 100–120 kV, this may not be seen (*6*).

Early intubation is essential at the first sign of oedema or pulmonary failure. Adequate oxygenation is essential, and the mode of ventilation will need to be assessed for each individual (*6*, *8*, *9*).

Pulmonary function tests and chest X-rays should be conducted on patients at follow-up after 2–3 months.

Stability/neutralization
Phosgene is very persistent in the atmosphere. As it does not absorb UV light, it does not undergo photolysis by sunlight in the troposphere but should photolyse at higher altitudes. The half-life in the atmosphere is estimated to be 113 years at sea level.

Phosgene reacts with hydrogen in water, and with primary and secondary amines.

The water solubility and vapour pressure of phosgene are such that it will volatilize rapidly from water.

Protection
This can be provided by a military-type respirator.

2.1.2 *Chloropicrin*

Also known as trichloronitromethane or nitrochloroform (CAS Registry Number 76-06-2), chloropicrin is both a lacrimator and a lung irritant. It is an oily liquid, colourless or yellowish green, at all ambient temperatures, with a highly irritating vapour. It will not burn but can decompose at high temperatures forming toxic gases such as phosgene, hydrogen chloride, nitrogen oxides and carbon monoxide. For chemical-warfare purposes, chloropicrin has been used as a casualty agent, a harassing agent and a training agent.

Sources

Chloropicrin was first prepared in 1848 from picric acid and bleach. Nowadays it is made by chlorinating nitromethane. Its peaceful applications include use as an insecticide, rodenticide and fumigant. Its former application as a riot-control agent is now rare.

Exposure
Exposure to chloropicrin is primarily through inhalation and direct contact. Concentrations of 0.3–1.35 ppm will result in painful eye irritation in 3–30 seconds, depending on the susceptibility of the individual. A 30-minute exposure to a concentration of 119 ppm and a 10-minute exposure to 297.6 ppm both resulted in the death of the individual exposed. Higher concentrations will be lethal following shorter exposure periods.

The odour threshold of chloropicrin is 1.1 ppm, above the level at which it will irritate the eye. Concentrations of 1–3 ppm will cause lacrimation.

Severe lung damage leading to pulmonary oedema and airways injury may occur. Oedema may be delayed and is exacerbated by physical activity. Complications of lung injury include secondary infections and bronchiolitis obliterans. Skin irritation is likely following direct contact, and may result in permanent scarring. Ingestion of small amounts will cause pain and is likely to result in nausea, gastroenteritis, and even death. The estimated lethal dose is 5–50 mg/kg body weight.

Chloropicrin is intermediate in toxicity between chlorine and phosgene. Chlorine in fatal concentrations produces injury primarily of the upper respiratory tract, trachea, and larger bronchi, whereas phosgene acts primarily on the alveoli. Chloropicrin causes greater injury to the medium and small bronchi than to the trachea and large bronchi. Alveolar injury is less than with phosgene, but pulmonary oedema occurs and is the most frequent cause of early deaths. Renal and hepatic damage following exposure has also been reported.

The permissible occupational exposure limit in the United States is 0.1 ppm as a time-weighted average over 8 hours.

Latency period and recovery time
Irritation of the eyes occurs rapidly and within 30 seconds following exposure to 0.3–1.35 ppm (2–9 mg/m^3). Concentrations of 1–3 ppm cause lacrimation, and a 1-minute exposure to 15 ppm will cause injury to the lung (*10*).

The effects of exposure may be delayed, but if oedema is not present after 48 hours, it is unlikely to occur.

If exposure is substantial, symptoms such as nausea, vomiting and diarrhoea may persist for weeks (*11*).

Individuals injured by inhalation of chloropicrin are reportedly more susceptible to the gas, and experience symptoms at concentrations lower than those that affect naive individuals.

Main clinical symptoms
Irritation of the eyes, nose and throat occur, resulting in lacrimation and coughing. Other symptoms reported in exposed individuals include vertigo, fatigue, headache and an exacerbation of orthostatic hypotension.

A concentration of 4 ppm for a few seconds renders an individual unfit for activity and 15 ppm for the same period has caused respiratory tract injury. Concentrations of 15 ppm cannot be tolerated for longer than 1 minute, even by individuals accustomed to chloropicrin.

Ingestion results in nausea, vomiting, colic and diarrhoea.

Inhalation is reported to cause anaemia in some individuals, and the haematopoietic system is also affected in animals exposed to chloropicrin, with reduced erythrocyte, haemoglobin and haematocrit (erythrocyte volume fraction) counts (*12*).

Asthmatics exposed to chloropicrin will experience asthma attacks because of its irritant properties.

Auscultation of the lungs may reveal moist diffuse rales, but these will be present only in the most severe cases. X-ray examination of the chest may show diffuse infiltration of lung fields.

Toxic pulmonary oedema will be more severe, and appear earlier if patients undertake physical activity after exposure.

Long-term health implications
Data are inadequate to assess whether chloropicrin causes developmental, reproductive or mutagenic effects. In a carcinogenicity study in rodents, animals were exposed for too short a period to enable an assessment of carcinogenic risk to be made. Data on mutagenicity are equivocal: chloropicrin is mutagenic to bacteria but not to mammalian cells.

Detection
A range of analytical methods are available for detection purposes, including chemical assays and combinations of gas chromatography, ion-selective electrode, electron capture, spectrometry and polarography (*13*, *14*).

Principles of medical management
Patients should be removed from the source of the exposure and clothing loosened. The airway should be checked to ensure that it is clear. Patients should be observed for 48 hours, checking for hypoxia or hypercarbia; if oedema develops, it will be apparent by this time. Warmth, rest and quiet are vital for all patients.

Prophylaxis/treatment
If skin contamination occurs, the affected areas should be washed with soap and tepid water. Washing may need to be done for 20–30 minutes, and any contaminated clothing removed.

If there is contact with the eyes, they should be washed with copious amounts of tepid water for up to 20 minutes. If irritation persists, the irrigation should be repeated.

If chloropicrin is ingested, vomiting should not be induced. The patient should be encouraged to drink water or fluids.

Oedema may be delayed following inhalation but should be detectable by 48 hours. Positive airway pressure will assist breathing. Oxygen should be administered if the patient is hypoxic or cyanosed. Bacterial infection is common with oedema, and careful surveillance cultures are required. Prophylactic antibiotics are not recommended. Fluids should be administered if the patient is hypotensive.

Stability/neutralization
Chloropicrin decomposes to give phosgene, nitrosyl chloride, chlorine and nitrogen oxides on exposure to light. Heating above 150 °C causes decomposition to phosgene and nitrosyl chloride. Chloropicrin reacts violently with alkali or alkaline earths. It is sparingly soluble in water (2.2 g/litre).

If fire breaks out in the vicinity of chloropicrin, the area concerned should be approached from upwind. Water (in flooding conditions or as fog or foam), dry chemicals or carbon dioxide should be used to extinguish fires.

If spills occur, these should be contained with sand/soil or absorbent material, which should then be shovelled into a suitable container. Care must be taken in flooding an area with water as this may react with the acid chloropicrin. Large quantities of water can be added safely to small quantities of chloropicrin.

Protection
Any air-purifying, air-supplying, or chemical-cartridge full-face mask will provide adequate protection.

2.1.3 *Perfluoroisobutene*

Also known as 1,1,3,3,3-pentafluoro-2-(trifluoromethyl)-1-propene (CAS Registry Number 382-21-8) or PFIB, perfluoroisobutene is a rapid-acting lung irritant that damages the air–blood barrier of the lungs and causes oedema. Microscopic oedema is evident in pulmonary tissues within 5 minutes. It is a colourless, odourless gas at most ambient temperatures and is easily liquefied.

Sources
PFIB does not occur naturally. It is a by-product of the manufacture of polytetrafluoroethylene (Teflon) and is also formed when this type of polymer or the related perfluoroethylpropylenes are heated to temperatures that cause thermal decomposition. The fumes generated in decomposition contain PFIB. Teflon generates PFIB-containing fumes at temperatures in excess of 360 ^{o}C (*15*).

The properties of organofluoride polymers, which include lubricity, high dielectric constant and chemical inertness, are such that these materials are used extensively in military vehicles such as tanks and aircraft.

Exposure
Inhalation is the principal route of exposure. High concentrations may produce irritation of the eyes, nose and throat. The lung is the main target organ and the only one reported in human studies. Systemic effects seen in animal studies occur only where there is substantial injury to the lung, and hypoxia is considered to be a major contributing factor.

Data on dosages causing symptoms in humans are sparse and, where effects have been reported, individuals have been exposed to a range of other gases as well as PFIB.

In rodents, dosages of 150–180 ppm.min (1250–1500 mg.min/m^3) will kill 50% of the test population. Comparable dosages for phosgene are 750 ppm.min (*16*, *17*).

Latency period and recovery time
A syndrome known as "polymer fume fever" has been described following inhalation of the pyrolysis products of organofluorides. Exposure to fumes has occurred when Teflon has been heated directly in welding processes and indirectly when cigarettes contaminated with micronized Teflon have been smoked (*15*, *18*, *19*). Symptoms may appear 1–4 hours post-exposure and are often mistaken for influenza. Subsequent symptoms are those of pulmonary oedema with, initially, dyspnoea on exertion, followed by difficulty in breathing unless seated or standing and, later, dyspnoea at rest. Oedema, as shown by clinical and radiological evidence, becomes more marked for up to 12 hours, before it clears, with recovery usually complete by 72 hours.

Main clinical symptoms
High concentrations in animals have caused sudden death, but this has not been recorded in humans.

Irritation of the eyes, nose and throat may occur if the concentration is high enough. At lower concentrations, a sense of discomfort in the chest, especially on taking a deep breath, may be the first symptom. There may be a feeling of irritation or oppression retrosternally, but is usually not severe enough to be described as pain. A dry irritating cough may or may not develop and worsen as the chest becomes increasingly sore. However, these preliminary symptoms may be absent, and the first warning of illness may only be a general malaise.

A few hours after exposure, there is a gradual increase in temperature, pulse rate and (possibly) respiration rate. Shivering and sweating usually follow. Temperatures are reported not to exceed 104 ^{o}F (40 °C) and pulse-rate is generally below 120.

Physical signs are fleeting. Auscultation of the lungs may reveal diffuse, moist rales, but these are usually present only in the most severe cases. X-ray examination of the chest may show diffuse infiltration of lung fields.

Toxic pulmonary oedema may be more severe and appear earlier if the patient exercises post-exposure.

Two human deaths from pyrolysis products of polymerized organofluorides have been reported (*16*).

Long-term health implications
Several reports of decreased pulmonary function, including reduced carbon monoxide perfusion rate, have been documented in humans up to 6 months after exposure to polymer fume.

In one reported case, a 50 year-old woman experienced some 40 episodes of polymer fume fever mainly related to smoking organofluoride-contaminated cigarettes, and 18 months after her last bout she was found to have progressive exercise dyspnoea. Pulmonary function tests supported a provisional diagnosis of alveolar capillary block syndrome, with decreased carbon monoxide perfusion, increased difference with exercise between the alveolar and the arterial partial pressure, and minimal airway disease. Cardiopulmonary physical examination, chest radiograph and arterial blood gases were normal, but the woman died 6 months later from a ruptured berry aneurysm and a subarachnoid haemorrhage. Histological examination of the lungs revealed moderate interstitial fibrosis. Alveolar septae were thickened by dense collagen with only focal, minimal chronic inflammatory cell infiltration. The bronchi were normal (*20*).

No data are available on the genotoxicity, mutagenicity or carcinogenicity of PFIB.

Detection
Gas samples can be collected by using an adsorbent filter either passively or with the aid of a pump. Laboratory analysis can be effected by gas chromatography.

Principles of medical management
Victims should be removed from the source of exposure and clothing loosened. Airways should be checked to ensure adequate clearance. Patients should be observed for 48 hours, checking for hypoxia and hypercarbia; if oedema develops, it will be apparent by this time. Warmth, rest and quiet are vital for all patients.

Prophylaxis/treatment
There is no recognized prophylaxis for human PFIB exposure. Protection against the lethal effects of inhaled PFIB has been demonstrated in rats when *N*-acetylcysteine was administered orally 4–8 hours before gas exposure. The duration of protection was related to the plasma concentrations of thiol compounds (cysteine, glutathione and *N*-acetylcysteine) derived from the *N*-acetylcysteine administered (*21*). No post-exposure medical or chemical therapy that impedes or reverses injury from PFIB inhalation is known (*16*).

Early oedema may be detected by chest X-ray (and before clinical signs appear) using 50–80 kV. Pulmonary oedema responds clinically to the application of positive airway pressure. PEEP (positive-end expiratory pressure)/CPAP (continuous positive airway pressure) masks are of value initially. Intubation may be necessary. Oxygen should be

administered if the patient is hypoxic or cyanosed. Fluid replacement is mandatory when the patient is hypotensive. Combined hypotension and hypoxia may damage other organs. Bacterial infection is common, and careful surveillance cultures are required. However, routine prophylactic antibiotics are not recommended. Steroid therapy has been used in two instances of PFIB exposure of the same worker. Since recovery is often spontaneous, assessing the value of steroid use is difficult (*16*).

Stability/neutralization
When dissolved in water, PFIB decomposes rapidly to form various reactive intermediates and fluorophosgene, which, in turn, decomposes to give carbon dioxide, a radical anion and hydrogen fluoride (*22*).

Protection
A military-type respirator can be used but some types may not be effective, since the advantage of PFIB as a chemical warfare agent is that it is poorly adsorbed by charcoal.

2.2 Blood gases

Lethal chemical agents that interfere with cell respiration have come to be known as blood gases. This is a reference to the mode of action of cyanides, which were believed to interfere with oxygen uptake from the blood (or carbon dioxide exchange between blood and tissues and between blood and the air in the lungs). The key agent is hydrogen cyanide, a toxic industrial chemical that has also been used as a chemical-warfare agent. Another such chemical, not described here, is cyanogen chloride.

2.2.1 *Hydrogen cyanide*

Also known as hydrocyanic acid (CAS Registry Number 74-90-8) or HCN, hydrogen cyanide is a rapid-acting lethal agent that inhibits aerobic respiration at the cellular level, preventing cells from utilizing oxygen (*23*). Liquid HCN, which at atmospheric pressure occurs over the temperature range –14 °C–+26 °C, is colourless to yellowish brown in appearance. On standing, it polymerizes and may explode, though it can be stabilized. Some people can smell HCN at low concentrations, describing an aroma of bitter almonds or marzipan; others cannot detect it.

Sources
Hydrogen cyanide is widely available in the chemical industry as an intermediate. It is used as a pesticide, rodenticide, fumigant and, in certain countries where capital punishment is still practised, as an instrument of state killing. More general exposure to cyanide occurs through tobacco smoke, smoke inhalation from fires and, in sub-Saharan Africa, from cyanide-glycosides in the cassava tuber (*24*).

Exposure
Inhalation is the most likely route of entry, causing hyperventilation initially. HCN vapour does not cross skin. Liquid HCN will penetrate skin, as may aerosols.

Although cyanides are rapidly detoxified by sulfur transferase enzymes, these are unlikely to play a significant role in acute poisoning, as occurs on the battlefield. Detoxification is important at lower concentrations, and exposure to 60 mg/m^3 may not cause any serious symptoms. At 200 mg/m^3, death occurs after 10 minutes. Above 2500 mg/m^3, and certainly above 5000 mg/m^3, death is likely within 1 minute (*25*).

Latency period and recovery time
Symptoms of poisoning are rapid in onset since the gas is quickly absorbed from the lungs. Hyperventilation occurs first and increases with the dose inhaled. This is followed by rapid loss of consciousness at high concentrations.

Main clinical symptoms
The toxicity of HCN is largely attributable to the inhibition of cytochrome oxidase, which results in interference with aerobic respiration in the cell by preventing oxygen from being utilized. Lactic acid accumulates, and cells die from histotoxic anoxia. Intracellular calcium concentrations increase before cell death, a mechanism not specific to cyanide, as the phenomenon is seen in most cells before they die.

Hyperventilation is the principal initial symptom at very high concentrations, followed by loss of consciousness, convulsions and loss of corneal reflex, death being caused by cardiac and/or respiratory arrest.

At high concentrations, victims notice a sensation of throat constriction, giddiness, confusion and poorer vision. Temples on the head feel as though gripped in a vice, and pain may occur in the back of the neck and chest. Unconsciousness follows and the individual falls. Failure to remove the victim from the HCN atmosphere will result in death in 2–3 minutes, preceded by brief convulsions and failure of respiration (*26*).

At lower but still lethal concentrations, symptoms may increase in severity over an hour or longer. Victims notice an immediate and progressive sense of warmth (due to vasodilation) with visible flushing. Prostration follows, with nausea, vomiting, probable headache, difficulty in breathing and a feeling of tight bands around the chest. Unconsciousness and asphyxia are inevitable unless exposure ceases.

At low concentrations (or doses), individuals may feel apprehensive, experience dyspnoea, headaches and vertigo, and notice a metallic taste in the mouth.

Long-term health implications
There are no long-term health implications at low concentrations. Tropical ataxic neuropathy, seen in victims of chronic cyanide poisoning caused by the consumption of poorly processed cassava, is not relevant to HCN exposure in warfare.

At near lethal concentrations, the effects of HCN on cellular respiration are likely to affect brain function. Deterioration in intellect, confusion, loss of concentration and parkinsonian symptoms are possible.

Detection

A number of analytical methods are available for use in detection. Laboratory detection (and detection in mobile field vehicles) is by gas chromatography–mass spectrometry (GC-MS).

Cyanide is rapidly removed from blood and converted by the enzyme rhodanase into the less toxic thiocyanate, which can be measured in urine.

Principles of medical management
The patient should be removed from the source of exposure. The rapidity of action of HCN may mean that those arriving on the scene will find casualties who are asymptomatic; showing acute symptoms; recovering from them; or dead. Triage should be performed.

Victims who are asymptomatic several minutes after exposure do not require oxygen or antidotes.

Where exposure has caused acute effects (convulsions, apnoea), oxygen and antidotes should be administered immediately.

Patients recovering from acute exposures (and unconscious, but breathing) will make a faster recovery with antidotes and oxygen (27).

Resources permitting, resuscitation should be attempted on subjects with no pulse in case heart stoppage is recent.

Decontamination of clothing or equipment is unnecessary in view of the high volatility of HCN.

Prophylaxis/treatment
This is likely to be complicated on the battlefield. Exposed troops cannot be expected to self-administer antidotes (*25*).

Treatment must be prompt. After oxygen has been administered, subsequent treatment is aimed partly at dissociating the cyanide ion from cytochrome oxidase. Therapies include sodium thiosulfate (to increase rhodanase activity), sodium nitrite or 4-dimethylaminophenol (4-DMAP) (to form methaemoglobin, which in turn combines with cyanide to form cyanmethaemoglobin) or cobalt (which also combines with cyanide ions) (*27–29*).

Stability/neutralization
HCN is unstable and non-persistent, and degrades slowly in the atmosphere. It can travel long distances, and its concentrations will fall as the distance travelled increases. It mixes with water and decomposes slowly.

Protection
A military-style gas mask with filters treated so as to adsorb cyanide should be used.

2.3 Vesicants

The vesicants, or blister agents, are general tissue irritants with an additional systemic action. Contact with skin tissues provokes blistering in the affected region after some delay. Contact with the eyes causes more rapid injury and leads to inflammation and possible temporary loss of sight. Injury to the respiratory tract occurs, the nature of the injury varying with the agent.

The two main groups of vesicants are the dichloroarsine derivatives and the so-called "mustards". The latter are militarily the more important as they lack the initial irritant effect of the dichloroarsines and have odours that are much less readily detected, so that they are well suited to insidious attack. The dichloroarsines will cause pulmonary oedema (toxic alveolitis), whereas this is not a typical feature of mustard gas exposure. All the mustards contain at least two 2-chloroethyl groups, attached either to thioether residues (the sulfur mustards) or to amine residues (the nitrogen mustards).

2.3.1 *Mustard gas*

Also known as bis(2-chloroethyl) sulfide (CAS Registry Number 505-60-2), yperite or Lost, mustard gas is a colourless to amber oily liquid of neutral reaction, freezing at 14 °C when pure and boiling at 228 °C with slow decomposition. At high concentrations, it has a pungent odour resembling that of horseradish, onions or garlic, much of which may be due to contamination with ethyl sulfide or similar by-products of its synthesis. It is only slightly soluble in water, but may dissolve in organic solvents and fats. Chemically and physically, it is a relatively stable substance. When dissolved in water, it first hydrolyses and then oxidizes to the less toxic sulfoxide and sulfone.

Sources
Sulfur mustard had been synthesized by 1860 and was developed as a chemical warfare agent during the First World War. It has practically no other application.

Exposure
Exposure to both liquid and vapour occurs, mainly via inhalation and by skin contact. Mustard gas produces militarily significant effects over a wide range of dosages. Incapacitating eye injury may be sustained at about 100 mg.min/m^3. Significant skin burns may begin at 200 mg.min/m^3. The estimated respiratory lethal dose is 1500 mg.min/m^3. On bare skin, 4–5 g of liquid mustard gas may constitute a lethal percutaneous dosage, while droplets of a few milligrams may cause incapacitation.

Mustard gas vapour can be carried long distances by the wind. Local contamination of water exposed to sulfur mustard may occur, liquid mustard tending to sink as a heavy oily layer to the bottom of pools of water, leaving a dangerous oily film on the surface.

Toxic concentrations of mustard gas in the air smell, the odour being detectable at about 1.3 mg/m^3. Experience in the First World War and in the Iran–Iraq war in 1980–1988 has clearly shown the incapacitating effects of mustard gas secondary to the lesions of skin and mucosa. Only a limited number of cases — 2–3% among about

400 000 exposed during the First World War (*25*) and a similar percentage in the Iran–Iraq conflict — have a fatal outcome, mainly within the first month.

Latency period from exposure to symptoms
Under field conditions without protection, signs and symptoms develop gradually after an interval of several hours. The duration of this interval depends on the mode of exposure, the environmental temperature, and probably also on the individual.

Quite soon after exposure, however, nausea, retching, vomiting and eye smarting have occasionally been reported. Acute systemic effects, central nervous excitation leading to convulsions and rapid death occur only at supra-lethal dosages.

Main clinical symptoms
Signs and symptoms usually develop in the following order. The first definite symptoms generally occur in the eyes between 30 minutes and 3 hours after exposure, starting with a feeling of grittiness, progressive soreness and a bloodshot appearance, and proceeding to oedema and all the phenomena of acute conjunctivitis, with pain, lacrimation, blepharospasm and photophobia. There is increased nasal secretion, sneezing, sore throat, coughing and hoarseness, and dyspnoea may develop. Within 4–16 hours after exposure, these symptoms become much more marked and distressing: the eyes begin discharging and are very painful, the nasal discharge is more purulent, and the voice is husky or suppressed. Nausea, retching and vomiting, associated with epigastric pains, occur in a large proportion of subjects and may recur at frequent intervals for several hours. In severe cases, they may become intense and prolonged. Diarrhoea may set in, but is rather unusual. The skin may begin to itch during this period and skin rashes may show as a dusky erythema of the exposed parts of the body and the axilla and genitals, with blisters beginning to appear. At the end of 24 hours, all these symptoms may have increased in severity, but death almost never occurs during the first day.

Evolution and recovery
In mild cases, skin lesions may remain limited to an erythema, which turns black in about 10–15 days, while the superficial epidermal layers desquamate without causing an actual skin defect. This phenomenon, already known from the First (*26*, *30*) and Second (*31*) World Wars, was also observed in Iranian casualties (*32*). With moderate to severe exposure, large blisters develop, filled with a clear yellow fluid, which usually break, leading to erosions and full-thickness skin loss and ulceration. Blisters caused by mustard gas may heal in 2 or 3 weeks, and full-thickness erosions after 6–12 weeks. On and around the burned area, hyperpigmentation occurs. The site of healed mustard burns is hypersensitive to mechanical trauma.

In severe cases, inflammation of the upper and lower respiratory tract becomes conspicuous during the second day. The expectoration becomes abundant, mucopurulent, sometimes with large sloughs of tracheal mucosa. This is complicated by secondary infection of the necrotic respiratory membranes. Fever sets in, with rapid pulse and respiration. The infection may terminate in bronchopneumonia, with death at any time between the second day and the fourth week. Recovery is slow, and expectoration and cough may persist for several weeks.

Sulfur mustard is absorbed and distributed systemically. In severe cases, after a brief period of increasing white blood cell count in peripheral blood, a rapid fall takes place. In Iranian casualties from the Iran–Iraq war, leukopenia was observed between day 5 and day 20 after exposure. Severe leukopenia was accompanied by sepsis, cardiovascular shock and multi-organ failure.

Experience with Iranian casualties showed that in, in those with severe lung complications requiring artificial ventilation, and where there was substantial systemic exposure leading to severe leukopenia, prognosis was very poor, even when sophisticated treatment was available (*32*).

Long-term health implications
Recent experience after the Iran–Iraq war confirmed that long-term skin lesions — mainly scarring of the skin, and hyper- and hypopigmentation — itching, and lung diseases, such as chronic obstructive bronchitis and emphysema, could develop (Sohrabpour, Doulati & Javaadi, personal communication, 1999).

A most distressing phenomenon, known from the First World War but now also observed after the Iran–Iraq war, is the development of delayed keratitis of the eye after an interval of 6–10 years with late-onset blindness. The lesions recur even after corneal transplantation (Javaadi, personal communication, 1999).

Both sulfur and nitrogen mustards have been shown to be mutagenic, carcinogenic and teratogenic under both in vitro and in vivo experimental conditions. Studies undertaken on mustard gas factory workers in Japan and the United Kingdom demonstrated the carcinogenic effect in humans. Exposures to mustard gas in factories may have been both considerable and prolonged. A more difficult question concerns the likelihood of developing cancer as a result of exposure to sulfur mustard on the battlefield. Here the evidence is suggestive but not absolutely clear-cut (*25*). Although 11–14 years have, at this writing, passed since the employment of mustard gas in the Iran–Iraq war, no increase in cancer incidence has so far been observed in exposed soldiers (Keshavarz, personal communication, 1999), but it is still too soon for definite conclusions.

Detection in the field and diagnosis of exposure
A number of techniques are available to detect liquid sulfur mustard, e.g. by means of detection paper, powder or chalk. Sulfur mustard vapour in air can be detected by the use of vapour-detection kits or by means of automated chemical agent detectors employing either ion-mobility spectrometry or flame photometry.

In the diagnosis of exposure to sulfur mustard in humans, alkylation products of sulfur mustard with haemoglobin, albumin and DNA in blood, as well as metabolites of sulfur mustard in urine, have proved to be useful targets.

Based on a monoclonal antibody that was raised against the major adduct of sulfur mustard in human DNA, namely the adduct at the 7-position of guanine, enzyme-linked immunosorbent (ELISA) and immunoslotblot assays have been developed. With haemoglobin, the adducts with the amino function in terminal valine of the α- and β-chains have proved to be most convenient for diagnosis. In principle, the

immunoassay approach has been developed for use under field conditions, whereas the mass-spectrometric methods can be used to confirm the immunochemical result under more sophisticated conditions. In view of the long biological half-life of the protein adducts, the mass-spectrometric methods are highly useful for retrospective detection of exposure. Both the mass-spectrometric and the immunoassay methods have been successfully applied to blood samples taken from Iranian soldiers during the Iran–Iraq war more than 3 weeks after alleged mild exposure to sulfur mustard (*33*).

Metabolism of sulfur mustard leads to a complicated mixture of products excreted into the urine. Contrary to the widely held belief, the hydrolysis product of sulfur mustard, namely thiodiglycol, is only a minor metabolite in urine. However, the sulfoxide derivative of thiodiglycol is abundantly present. This is reduced to thiodiglycol for GC–MS analysis. Unfortunately, both thiodiglycol and its sulfoxide are often present in the urine of unexposed persons. β-Lyase activity on bis-cysteinyl conjugates of sulfur mustard (presumably derived from glutathione adducts) leads to the excretion of two sulfoxide/sulfone metabolites that can be reduced to thioether derivatives for subsequent GC–MS analysis. These products are not present in the urine of unexposed persons and were found in that of two male subjects who had suffered from extensive blistering due to accidental exposure to sulfur mustard (*34*).

Principles of medical management

Adequate first-aid measures are very important. Attendants should wear protective clothing and respirators when dealing with contaminated casualties. Patients should be removed from the source of contamination, and areas of liquid contamination should be decontaminated. Liquid contamination of the eyes should be immediately rinsed out, using copious amounts of normal saline or water from any source.

Prophylaxis/treatment

No prophylactic treatment against mustard gas is available, prophylaxis depending entirely on the protection of skin and airways by adequate protective garments. Treatment is symptomatic.

As far as skin lesions are concerned, different patterns of management have been used, ranging from treating exposed persons at burns units to treating by bathing and the use of wet dressings. Calamine lotions have been used for erythema and minor blistering, chloramine 0.2% or 0.3% solutions or silver sulfadiazine (Flamazine) 1% cream for preventing secondary infections of the skin lesions, and local corticosteroid solutions to reduce itching and irritation. Systemic analgesics, from paracetamol to morphine, and systemic antihistamines or corticosteroids have also been used. In one patient with large full-thickness burns, skin grafts were applied and were found to take well (*25*). Several days after exposure, removal of the surface of the skin in the affected area until capillary bleeding occurs (dermal abrasion) may hasten recovery from the lesions (*35*).

Eye lesions should be treated by saline irrigation, petroleum jelly on follicular margins to prevent sticking, local anaesthetic drops to relieve severe pain (though these may damage the cornea) or, better still, systemic narcotic analgesics. To prevent infection,

chloramphenicol eye drops or another local antibiotic should be used. In cases of severe eye damage, an ophthalmological opinion must be sought.

Inhalation of moist air was used in the treatment of Iranian casualties in the Iran–Iraq war, and acetylcysteine was used as a mucolytic. Bronchodilators have also been used. Antibiotic cover is recommended in view of the risk of secondary infection.

Bone-marrow depression leading to severe leukopenia and aplastic anaemia should be treated with granulocyte, platelet and red cell transfusions. Whether drugs that stimulate normal marrow are of any use is not known. Granulocyte colony-stimulating factor and related factors should be considered in severe leukopenia, but it is not known whether they would be useful (*25*).

In order to eliminate sulfur mustard from the circulation and from the body in general, administration of thiosulfate and other thiols, as well as haemodialysis and haemoperfusion, have been used in some Iranian mustard gas casualties. There is, however, no established place for them in the treatment of mustard gas intoxication. Moreover, since there is no sound theoretical basis for haemodialysis and haemoperfusion, as no active mustard has been identified in blood taken from victims, and since, with both procedures, there may be a risk of bleeding and of secondary infection in these immunocompromised patients, these procedures should not be applied (*32*).

In severely ill patients, appropriate intensive care measures are necessary.

Stability/neutralization
Sulfur mustard can be quite persistent in the environment, depending on the temperature. It represents a serious persistent hazard, particularly at temperatures below 0 °C. Substances such as metal, glass and glazed tiles are generally impervious to mustard, although painted surfaces may take it up for a time and then release it later. Decontamination procedures for skin, equipment and materiel have been developed by most armies, using neutralizing, active chemicals, such as chloramine solutions, or neutral adsorbing powders, e.g. fuller's earth. The use of plain water for decontamination, e.g. by showering, is of dubious value since it can disperse the agent over the body.

Protection
Military-type active-carbon-containing protective clothing and a full-face gas mask with an appropriate filter should be used.

2.3.2 *Lewisite*

Also known as 2-chlorovinyldichloroarsine (CAS Registry Number 541-25-3), lewisite is an odourless, colourless oily liquid, freezing at –18 °C and boiling at 190 °C. Technical preparations are often blue-black in colour and smell like geraniums. They will usually also contain lewisite-2 (*bis*(2-chlorovinyl)chloroarsine) and lewisite-3 (*tris*(2-chlorovinyl)arsine). Lewisite is practically insoluble in water but

freely soluble in organic solvents. It hydrolyses rapidly when mixed with water or dissolved in alkaline aqueous solutions such as sodium hypochlorite solution.

Sources
Lewisite was studied as a potential chemical-warfare agent before 1918, but there has been no verified use on a battlefield except where it has served as a freezing-point depressant for mustard gas. It has essentially no applications for peaceful purposes.

Exposure
Exposure may occur to liquid and vapour, via inhalation and by skin contact. Lewisite is about 7 times less persistent than mustard gas. Acute toxicity figures for humans are not well known, but 0.05–0.1 mg/cm^2 produces erythema, 0.2 mg/cm^2 produces vesication and a 15-minute exposure to a vapour concentration of 10 mg/m^3 produces conjunctivitis. About 2.5 g, if applied to the skin and not washed off or otherwise decontaminated, would be expected to be fatal to an average 70-kg person because of systemic toxicity. On inhalation, the LCt_{50} [inhalational toxicity of the vapour form, where C is concentration measured in mg/m^3 and t is the time of exposure measured in minutes] in humans is estimated to be about 1500 $mg.min/m^3$.

Latency period, and main clinical symptoms
The latency period from exposure to symptoms appears to be shorter with lewisite than with mustard gas. Otherwise, as seen in accidental exposures, lewisite produces a similar clinical picture. There is immediate eye irritation and blepharospasm, rapidly followed by coughing, sneezing, lacrimation and vomiting. On skin contact, a burning sensation is felt, and the erythema and vesication, following after a few hours, are painful. Maximal blister size, covering the whole erythematous area, develops over 4 days. Abnormal pigmentation does not occur. Breathing may be difficult, followed in severe cases by pseudomembrane formation and pulmonary oedema. Liver toxicity and systemic arsenic toxicity—diarrhoea, neuropathy, nephritis, haemolysis, shock and encephalopathy—may follow after extensive skin contamination. Eye lesions may be particularly serious with blindness following unless decontamination is very prompt.

Evolution and recovery
Healing of skin lesions proceeds in a few weeks and more readily than in the case of mustard lesions, unless there has been secondary infection. Secondary bronchopulmonary infections may occur, whereas recovery from systemic toxicity will depend on the severity of the initial lesions. Lewisite seems not to be mutagenic, teratogenic or carcinogenic.

Detection in the field and diagnosis of exposure
The detection and identification of lewisite in the environment are much more difficult than for sulfur mustard. It cannot be detected by automated chemical agent detectors, although laboratory identification by gas chromatography, after derivatization, is possible. As with sulfur mustard, techniques based on protein adducts might become available, more especially the quantification of the metabolite 2-chlorovinylarsonous acid bound to haemoglobin and detectable in blood 10 days after subcutaneous administration to experimental animals. Unbound 2-

chlorovinylarsonous acid may be measured in urine for up to 12 hours after exposure (*36*).

Principles of medical management
Adequate first-aid measures are very important. Attendants should wear protective clothing and respirators when dealing with contaminated casualties. Patients should be removed from the source of contamination, and areas of liquid contamination should be decontaminated. Liquid contamination of the eyes should be immediately rinsed out using copious amounts of normal saline or water from any source.

Prophylaxis/treatment
No prophylactic treatment against lewisite is available, so prophylaxis depends entirely on protection of the skin and airways by adequate protective clothing and by early decontamination with fuller's earth or dilute solutions of bleach.

Treatment with dimercaprol (British anti-lewisite, BAL, 2,3-dimercaptopropanol) is the standard treatment for poisoning by arsenic compounds. It acts as a chelator by binding arsenic, and is available for deep, intramuscular injection, as a skin and eye ointment, and as eye drops (5–10% in vegetable oil). Local instillation in the eyes and intramuscular injections may be painful. Intramuscular doses are limited because of systemic toxicity. Several dosing regimens have been proposed, one of which prescribes 2.5 mg/kg, 4-hourly for four doses, followed by 2.5 mg/kg twice daily. Another scheme suggests 400–800 mg i.m. in divided doses on day 1, 200–400 mg i.m. in divided doses on days 2 and 3, and 100–200 mg i.m. in divided doses on days 4–12. The magnitude of the dose depends on body weight and the severity of the symptoms.

More recently, two water-soluble analogues of dimercaprol have been introduced in the clinic as arsenical antidotes, namely *meso*-2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS). They are less toxic than BAL and can be given orally; DMPS can also be given intravenously.

In severely ill patients, appropriate intensive care measures should be applied.

Decontamination/neutralization
Decontamination procedures for skin, equipment and materiel have been developed by most armies, using neutralizing, active chemicals, such as chloramine solutions, or neutral adsorbing powders, such as fuller's earth. The efficacy of decontamination by plain water, e.g. by showering, is dubious since it can disperse the agent over the body.

Protection
Military-type active-carbon-containing protective clothing and a full-face gas mask with an appropriate filter should be used.

2.4 The nerve gases

The designation “nerve gas” or “nerve agent” is used for organophosphorus and other organophosphate compounds that inhibit tissue cholinesterase in humans at small dosages. It is an allusion to the mode of action of these substances, namely the disruption of nerve impulse transmission. At the present time, two families of nerve gases are important for military purposes, namely the G agents, which are alkyl esters of methylphosphonofluoridic acid or of dialkylphosphoramidocyanidic acid, and the V agents, which are mainly alkyl esters of *S*-dialkylaminoethyl methylphosphonothiolic acid. G agents are primarily designed to act via inhalation, while V agents act primarily through skin penetration and the inhalation of aerosol.

Chemically and toxicologically, the nerve gases are similar to many of the commercial organophosphate pesticides and, while information on severe nerve gas poisoning in humans is rather limited, there are extensive data on human exposure to some of these pesticides. Insecticides such as tetraethyl pyrophosphate (TEPP) and parathion have caused a number of fatalities as a result of misuse or accidental poisoning.

Among the many different G and V agents, those that have in the past been manufactured in kilotonne quantities for chemical-warfare purposes are:

O-ethyl *N*,*N*-dimethyl phosphoroamidocyanidate	Tabun: CAS 77-81-6
O-isopropyl methylphosphonofluoridate	Sarin: CAS 107-44-8
O-1,2,2-trimethylpropyl methylphosphonofluoridate	Soman: CAS 96-64-0
O-ethyl *S*-2-(diisopropylamino)ethyl methylphosphonothiolate	VX: CAS 50782-69-9
O-isobutyl *S*-2-(diisopropylamino)ethyl methylthiophosphonate	VR: CAS 159939-87-4

Others have been produced, but in lesser amounts. Those produced in the largest quantities have been sarin and VR. In the account given below, however, VX is described rather than its isomer VR because the latter is still poorly characterized in the published literature. It would seem, however, that any differences in the properties of these two agents would be unlikely to invalidate the general picture presented.

Besides the G and V agents, there are several other chemical classes of organophosphate anticholinesterase agents that have been studied for chemical-warfare application. One such class, reported to have entered weaponization in the 1980s after discovery in the 1970s, is known as novichok. Published information on the novichok agents is, however, sparse. One characteristic is said to be a toxicity exceeding that of the V agents but the absence of a direct carbon–phosphorus bond in their molecular structure. The latter might mean, as some commentators have asserted publicly, that at least some novichoks do not figure in the schedules of the Chemical Weapons Convention.

2.4.1 *Sarin and VX*

Nerve agents are mostly odourless and colourless to yellow-brown liquids at ambient temperature, and are soluble in water. They hydrolyse quite rapidly in strongly alkaline solutions, while between pH 4 and pH 7 hydrolysis takes place very slowly. The water solubility of VX is in the range 1–5% at room temperature. It is more resistant to hydrolysis than sarin, particularly in alkaline solution.

Exposure
Nerve gases may be absorbed through any body surface. When dispersed as a vapour or aerosol, or absorbed on dust, they are readily absorbed through the respiratory tract or conjunctivae. Absorption is most rapid and complete through the respiratory tract.

The first effect observed on exposure to low air concentrations is miosis. For sarin, it appears in 50% of exposed men at about 3 mg.min/m^3. At about 10 mg.min/m^3, other muscarinic symptoms appear producing an incapacitating effect. Higher exposures become more and more incapacitating and are eventually lethal. Approximate figures for the concentration–time product that would be lethal to 50% of exposed men, are 150 mg.min/m^3 for tabun, 70–100 mg.min/$m^3$for sarin, 40–60 mg.min/$m^3$for soman and 50 mg.min/m^3 for VX (*25*).

Latency period
Exposure to nerve agent vapour dosages that were just lethal would probably result in death within one to a few hours. An exposure to several times the lethal dose would probably be fatal within several minutes to half an hour. Photographic evidence from Halabja in Iraqi Kurdistan suggests rapid death from exposure to what was most probably a sarin attack in March 1988. VX has been used in both a murder and an attempted murder. One man died on the fourth day after admission to hospital following an injection of VX into his neck (*37*). In an attempted murder, VX was sprayed on to the victim's back, necessitating a 15-day stay in hospital before his discharge, at which time he was suffering from amnesia and a neuropathy affecting the nerves that innervate the muscles of the shoulder girdle and upper extremities. By 6 months, the neuropathy had resolved but not the amnesia. There are significant differences in physiological responses to VX and sarin (*38*).

Main clinical symptoms
The effects of both nerve agents and organophosphate insecticides have been related to the inhibition of tissue cholinesterases at synaptic sites, and to an accumulation of excessive amounts of acetylcholine at nicotinic and muscarinic receptors in effector organs. These phenomena are followed by other disturbances of the nervous system. Numerous studies have demonstrated that the excitatory amino acid glutamate also plays an important role in the maintenance of organophosphorus-induced seizures and in the subsequent neuropathology, especially through an over-activation of the *N*-methyl-d-aspartate (NMDA) receptor subtype (*39*).

Muscarinic, nicotinic and central nervous system symptoms of nerve-gas poisoning, as listed by Grob (*40*), are given in Table A1.3. The time course of their appearance varies with the degree and route of absorption. After inhalation, bronchoconstriction

and respiratory distress appear before pronounced symptoms involving the gastrointestinal tract develop. Deaths from nerve agent poisoning can be attributed to respiratory and circulatory failure.

Evolution and recovery

After a single mild to moderate exposure, full recovery may take place. Moderate to severe poisonings necessitate treatment if there is to be survival. Inhibition of acetylcholinesterase is irreversible, but adaptation of synaptic transmission occurs. Spontaneous reactivation of the inhibited enzyme is almost non-existent in acute intoxication. If a patient survives for a number of hours or days there may be some spontaneous reactivation (with sarin, cyclohexyl sarin and VX but *not* with soman), provided that the agent does not persist and cause re-inhibition. Repeated daily exposures are cumulative and may result in severe poisoning.

Long-term effects

It is possible that persistent paralysis, organophosphate-induced delayed neuropathy (OPIDN), and axonal death followed by demyelination might develop among victims surviving many times the lethal dose of sarin. However, no such delayed effects have been observed among sarin survivors in the Islamic Republic of Iran.

Table A1.3. **Signs and symptoms of nerve-gas poisoning**[a]

Site of action	Signs and symptoms
Muscarinic	*Following local exposure*
Pupils	Miosis, marked, usually maximal (pin-point), sometimes unequal
Ciliary body	Frontal headache; eye pain on focusing; slight dimness of vision; occasional nausea and vomiting
Conjunctivae	Hyperaemia
Nasal mucosa membranes	Rhinorrhoea; hyperaemia
Bronchial tree	Tightness in chest, sometimes with prolonged wheezing, expiration suggestive of bronchoconstriction or increased secretion; cough
Sweat glands	Sweating at site of exposure to liquid
Nicotinic	
Striated muscle	Fasciculations at site of exposure to liquid
	Following systemic absorption
Muscarinic	
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion; dyspnoea, slight pain in chest; increased bronchial secretion; cough; pulmonary oedema; cyanosis
Gastrointestinal system	Anorexia; nausea; vomiting; abdominal cramps; epigastric and substernal tightness with "heartburn" and eructation; diarrhoea; tenesmus; involuntary defecation
Sweat glands	Increased sweating
Salivary glands	Increased salivation
Lacrimal glands	Increased lacrimation
Heart	Slight bradycardia
Pupils	Slight miosis, occasionally unequal; later, more marked miosis
Ciliary body	Blurring of vision
Bladder	Frequency; involuntary micturition
Nicotinic	
Striated muscle	Easy fatigue; mild weakness; muscular twitching; fasciculations; cramps; generalized weakness, including muscles of respiration, with dyspnoea and cyanosis
Sympathetic ganglia	Pallor; occasional elevation of blood pressure
Central nervous system	Giddiness; tension; anxiety, jitteriness; restlessness; emotional lability; excessive dreaming; insomnia; nightmares; headache; tremor; apathy; withdrawal and depression; bursts of slow waves of elevated voltage in EEG, especially on hyperventilation; drowsiness; difficulty in concentrating; slowness of recall; confusion; slurred speech; ataxia; generalized weakness; coma, with absence of reflexes; Cheyne-Stokes respiration; convulsions; depression of respiratory and circulatory centres, with dyspnoea, cyanosis, and fall in blood pressure.

[a] After Grob, 1963 (*40*).

Detection

Detection may be needed for the three basic purposes — alarming, monitoring and identification — and for some additional special purposes, e.g. miosis-level warning and food and water monitoring. There are now many examples of commercially available military equipment that is capable of performing the various detection tasks. The types of equipment range from manually operated wet chemical detection kits to advanced automatic equipment for specific CW agents. Military equipment is usually robust, of limited weight and size, and usually and increasingly designed for quick and easy operation.

Diagnosis of exposure

Apart from symptomatology, the measurement of decreased cholinesterase activity in blood is the only method currently available for the rapid diagnosis of exposure to nerve agents. However, this approach has several disadvantages, since it is nonspecific for nerve agents or even for organophosphate exposure. Moreover, it is useful only when >20% of inhibition has occurred, since blank values from the patient are usually not available.

Newer tests, which in the present state of development can be performed only in the laboratory, include: (i) analysis of intact or hydrolysed nerve agent in blood and/or urine; (ii) regeneration of nerve agent bound to proteins with fluoride ions and subsequent analysis of the phosphofluoridate; and (iii) hydrolysis of the phosphorylated protein and subsequent analysis of hydrolysed nerve agent and enzymatically formed metabolites thereof (*41–43*).

Principles of medical management

In severe cases of nerve agent poisoning, antidotal treatment *per se* may not be sufficient for survival. Assisted ventilation and general supportive measures will be required, sometimes for several days.

Prophylaxis/treatment

Prophylaxis and treatment will depend on the biochemical mechanism that has been identified.

Prophylaxis is based on the administration of a reversible anticholinesterase agent. Pyridostigmine, which is a carbamate used in myasthenia gravis, is proposed at doses of 30 mg, 3 times daily, aimed at producing a blood cholinesterase inhibition of about 30%. In cases of severe poisoning, these 30% protected cholinesterases will spontaneously reactivate and, assuming that the same phenomenon happens at the cholinergic synapses, the casualty will recuperate. (Reinhibition of the enzyme could occur if poison persists in the body and is available to bind to cholinesterases when pyridostigmine is removed). Further developments include a combination of the centrally acting carbamate physostigmine and the central-anticholinergic scopolamine to improve the protection of acetylcholinesterases in the central nervous system. They also include the administration of catalytic scavengers to capture the nerve agent in blood before it can be distributed into the organism.

Anticholinergic and anticonvulsant agents constitute a symptomatic drug therapy. Atropine sulfate blocks the muscarinic effects in the periphery, and partially

counteracts the convulsive effects and respiratory depression in the central nervous system. Loading doses range between 1 and 5 mg i.v. every 30 minutes until full atropinization, and maintenance doses of between 0.5 and 2 mg/hour. Titration of atropine in the individual patient must be carried out on the basis of the most relevant effects for a favourable clinical outcome, i.e. a decrease in bronchial constriction and secretions as judged by auscultation and blood gas analysis. Changes in heart rate are less important but easier to follow, and a mild tachycardia of 80 beats or more per minute should be maintained. Besides atropine, a centrally acting anticonvulsant should be administered, diazepam being the drug of choice. It is used to both prevent and treat convulsions. In addition to diazepam, lorazepam, midazolam and pentobarbital have been used to treat soman-induced seizures. Seizure control declines markedly if there is any delay in treatment; 40 minutes after exposure, control is minimal. Most clinically effective antiepileptic drugs may be incapable of terminating nerve agent-induced seizures (*44*). Because of the involvement of the glutaminergic system, the clinical utility of concomitant administration of an NMDA receptor blocker is currently under study.

Oximes, which are acetylcholinesterase reactivators, constitute a causal therapy. Most clinical experience has been gained with pralidoxime chloride, pralidoxime methanesulfonate or methylsulfate, and obidoxime chloride. More recently, the oxime HI6 (1-(2'-hydroxyiminomethyl-1'-pyridinium)-3-(4"carbamoyl-1"-pyridinium)-2-oxapropane dication) has been introduced by some countries. These agents relieve the important symptom of skeletal neuromuscular blockade but penetrate only poorly into the central nervous system. They can be administered as repeated injections or as a loading dose followed by a maintenance dose (*45*).

Stability/neutralization
Tabun, sarin and soman are quite volatile, whereas thickened soman and VX may persist in the environment, depending on temperature. VX represents a serious persistent hazard, particularly at temperatures below 0 °C. Decontamination procedures for skin, equipment and material have been developed by most armies, using neutralizing, active chemicals, such as chloramine solutions, or neutral adsorbing powders, e.g. fuller's earth.

Protection
Military-type active-carbon-containing protective clothing and a full-face gas mask with an appropriate filter should be used.

3. Disabling chemicals

Over most of the past century, disabling chemicals have been widely used, e.g. by police or other forces for law-enforcement purposes; by veterinarians to capture dangerous animals; by medical doctors to sedate or calm patients; by thieves and other criminals to disable victims; and by military forces to achieve tactical objectives with diminished loss of life. A particular chemical may be used for several of these purposes.

In the context of law enforcement, sensory irritants such as tear gases or sternutators have long been used by police forces to control civil disorder and are therefore often called "riot control agents" even when used for quite other purposes. The Chemical Weapons Convention, which states that "law enforcement including domestic riot control purposes" are among the "purposes not prohibited under this Convention", defines a "riot control agent" as "any chemical not listed in a Schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure". For law-enforcement purposes other than riot control, as in certain lawful types of anti-terrorist action, many toxic chemicals have been studied and occasionally used, including opioids and irritant agents. The CWC places no restrictions on what these chemicals may be other than that they should not be on Schedule 1 and that their types and quantities should be consistent with their purposes. In the case of chemicals held for use against hostage-takers, for example, or against persons threatening to detonate bombs, a key property is that the disablement should be extremely fast. However, the heterogeneity of any population that might be exposed to such a chemical is likely to mean that the dosage required for rapidly disabling all individuals will be lethal for some of them. Disabling chemicals initially studied for military purposes have sometimes found law-enforcement application, and vice versa.

Regarding military applications, defence authorities used to differentiate three classes of disabling chemical. *Class A*: agents that cause temporary physical incapacitation such as sleep, temporary paralysis, weakness, temporary blindness or serious respiratory disturbance and give no danger of death or permanent incapacitation. *Class B*: agents that in small doses cause temporary physical incapacitation, but that in large doses may cause death or permanent effects. *Class C*: agents that cause mental incapacitation. On this classification, a likely fatality rate exceeding 2% was taken as disqualifying an agent from any class of disabling chemical. The point about agents less lethal than this was that they might allow the high casualty rates or wide-area coverage effects available from more traditional chemical weapons to be exploited even when unprotected friendly forces or non-combatants were in the target area. When the classification was enunciated, in 1960, the examples cited of actual agents were the lacrimators CN and CS for Class A, the arsenical sternutator or vomiting agent adamsite for Class B, and the psychotropic agent LSD for Class C; meanwhile there was active research to identify disabling chemicals of greater military efficacy (*46*).

Since that time several new disabling chemicals have emerged. Among these are chemicals that cause physical incapacitation by psychotropic action, meaning that the distinction between Class A and Class C has faded. Examples include orivals, fentanyls and other opioids. The distinction between Class A and Class B was always less sharp than military authorities appeared to believe, for even an agent such as CS can cause serious damage to those who are exposed to abnormally high dosages or who are abnormally susceptible. That there is no such thing as a non-lethal or otherwise harmless disabling chemical has now become generally recognized.

The key distinction is now seen to lie in the duration of disablement. On the one hand is a chemical causing incapacitation that lasts for little longer than the period of

exposure — a characteristic of many irritant agents and the property that, in the civil context, makes it possible for disabling chemicals to be used by police forces to drive back rioters — and on the other is an agent causing incapacitation that lasts for a period of time substantially longer than that of exposure, thus providing a wider variety of possible actions for users of the weapon. Toxic substances in this longer-lasting category are commonly termed "incapacitants" or "incapacitating agents", although a new term, "calmatives", is starting to emerge. For the short-term category, "irritant" or "harassing agent" is a convenient label for the disabling chemicals concerned. In both categories, time to onset of disablement is also an important determinant of utility.

3.1 Incapacitants

Many chemicals can produce a non-fatal and prolonged but temporary incapacitation under controlled laboratory conditions, but few have yet been found that can be expected to do so under less controlled conditions. There are two main obstacles. Firstly, if fatalities are to be kept close to zero even in the immediate vicinity of the functioning munition, the agent must be one for which the incapacitating dosage is very much lower than the lethal dosage. Secondly, the agent must be one that can disable groups of individuals to an extent that is both significant from the user's point of view and predictable.

One class of potential incapacitating agents are the potent psychotropic drugs. These affect the central nervous system in a variety of ways so that the behaviour of exposed individuals is altered, rendering them incapable of performing military functions.

Interpreting the behaviour of a group of soldiers exposed to a psychochemical on the basis of experimental studies on subjects under controlled conditions is fraught with difficulties. Drug-induced behavioural changes in individuals are strongly influenced both by their environment and by the behaviour of other individuals in the vicinity. A drug does not always cause a behavioural change, particularly if there are persons in the vicinity who do not receive it. With LSD, for example, it has been demonstrated that drugged soldiers may behave in an apparently normal manner if they are in a unit with other soldiers who are not drugged. It would appear that the effects of a psychochemical on a group can be accurately predicted only if all of its constituent members receive a dose that would produce similar behavioural changes.

There is a more fundamental uncertainty, however, which results from the motivation of specific individuals. Where the motivation is powerful, subjects may accomplish complicated tasks even though they may be obviously quite severely drugged and behaving irrationally. Even though a drug might distort perception at an individual level, predicting the physical response and motivation of a drugged individual in a motivated fighting unit is much more difficult. Thus it is conceivable that, under the influence of a psychochemical, a combat unit is as likely to excel as it is to behave in an uncoordinated manner. Effects of exposure to psychochemicals in war are unknown, since experiments have been conducted only in peacetime. Motivation may be significantly different under fire.

In addition to behavioural effects, some psychochemicals will also cause physical incapacitation. Symptoms may include blurred vision, fainting, vomiting and incoordination. Two psychochemicals considered for weaponization and tested on many volunteers are reviewed below, but there are many other chemicals that alter mental function with and without accompanying somatic symptoms.

3.1.1 *Lysergide*

Also known as 9,10-didehydro-*N*,*N*-diethyl-6-methyl-ergoline-8-β-carboxamide (CAS Registry Number 50-37-3), *N*,*N*-diethyl-D-lysergamide or LSD, lysergide is a water-soluble solid, melting at around 198 °C, that is colourless, odourless and tasteless. It can be disseminated either as a contaminant of food or water or as an inhalable aerosol. It acts on the 5-hydroxytryptamine or serotonin pathway. As an agonist for the 5-HT2 receptor — a post-synaptic receptor — its effects are excitatory, resulting in release of serotonin, which in turn causes both mental and somatic symptoms (*47*).

Sources
Lysergide is widely available as an illegal drug.

Exposure
Lysergide is active following inhalation or after oral or intravenous administration.

The first symptoms of exposure are usually somatic and include mydriasis, dizziness, weakness, drowsiness, nausea and paraesthesia. They occur within a few minutes after either oral dosing or inhalation.

Altered mental states occur at doses as low as 25 µg. Following oral doses of 0.5–2.0 µg/kg, somatic symptoms, including dizziness and weakness, are seen within a few minutes. In the dose-range 1–16 µg/kg, the intensity of the psychophysiological effects are proportional to the dose. LSD is not an addictive substance. Lethal doses are estimated to be about 0.2 mg/kg (*48*).

Latency period and recovery time
Anxiety, restlessness, vomiting and general paraesthesias occur within 5 minutes following inhalation. Perceptual distortions begin some 30–60 minutes after oral ingestion. Peak effects occur 3–5 hours after exposure, and recovery is usually within 12 hours. Panic attacks are one of the more serious consequences of LSD exposure and usually last less than 24 hours, but can degenerate into prolonged psychotic states. LSD toxic psychosis can last from days to months. The psychosis is generally considered not to be caused by the LSD, but to be an exacerbation of an already underlying condition. LSD has a short half-life in humans of about 3 hours (*48*, *49*).

Anxiety, fatigue, movement into a dark environment, or use of marijuana can precipitate flashbacks, which may persist intermittently for several years after exposure to LSD.

Main clinical symptoms

Panic attacks are the most common adverse effect. Somatic effects are not consistent, are usually inconsequential and include: mydriasis; increased heart rate, blood pressure and reflexes; paraesthesias; twitches; incoordination; and skin flushing and sweating. Coma may occur at higher doses/exposures. Perceptual distortions occur, with altered sense of colour, shape and distance. Auditory and visual hallucinations are common. Emotional lability is frequently evident and often triggered by sensory clues.

The emotional and behavioural effects of LSD are different for each individual, and influenced by the local environment. Heightened arousal in a group situation may be seen as greater animation, talking and elation. In unusual surroundings with unfamiliar people, initial nervousness may well lead to anxiety.

Neuroleptic malignant syndrome leading to hyperpyrexia has been recorded in only one case and is therefore likely to be a rare event.

Long-term health implications
Evidence for teratogenic and embryo-lethal effects in animals is equivocal, with effects observed in some studies but not in others. LSD crosses the placenta and distribution of the chemical is similar in mother and fetus. There is no evidence that recreational use of LSD causes infertility in women.

Detection
Methods for the detection of LSD — usually developed for drug samples — include gas capillary column chromatography (GC), high-performance liquid chromatography (HPLC), and GC–MS. Radioimmunoassay techniques are available for detecting LSD in urine samples. Detection limits are as low as 5 pg/ml with GC–MS but usually higher with other techniques (*47*, *50*).

Principles of medical management
Patients should be removed from the source of exposure, assessed, stabilized and reassured.

Prophylaxis/treatment
No specific antidotes exist. Vital signs should be monitored and airway and circulation checked. Restraints should be avoided but care must be taken to ensure that patients do not injure themselves. They should be reassured and sedated with diazepam if necessary. Gastric lavage should be avoided if ingestion is the probable route of exposure as it is ineffective (LSD is absorbed rapidly) and may exacerbate psychotic reactions. For acute panic attacks, reassurance, support and reduction of sensory stimuli are the best management approaches. Patients should be placed in quiet environments, preferably with friends or familiar individuals. Sedation with diazepam (5–10 mg i.v.) may be needed. For acute psychotic reactions, haloperidol is the safest neuroleptic agent (but should be used only if essential). Phenothiazines should not be used as they may potentiate anticholinergic effects. Chlorpromazine should be avoided as this may cause cardiovascular collapse. Flashbacks should be treated with psychotherapy, and with anti-anxiety and neuroleptic drugs (*47*).

Stability/neutralization

LSD is soluble in water and degraded by ultraviolet light so that persistence in the environment is therefore unlikely.

Protection
A military-type gas mask provides protection against aerosols.

3.1.2 *Agent BZ*

BZ is the hydrochloride salt of 3-quinuclidinyl benzilate (CAS Registry Number 6581-06-2). It is a water-soluble solid melting at 239–241 °C. Its free base is a solid melting at 164–167 °C. Sometimes referred to as a psychochemical, BZ is an anticholinergic compound similar structurally and pharmacologically to atropine. It affects both the peripheral autonomic and the central nervous systems. It may be disseminated in aerosol form from solutions (*51*), pyrotechnically, or as a pre-sized powder.

Sources
3-Quinuclidinyl benzilate is produced commercially as an intermediate for the drug clidinium bromide.

Exposure
Inhalation is the most likely route, but BZ is also active by the intravenous, intramuscular and oral routes. As an aerosol, particle sizes in the 0.6–0.8 μm range are more effective than a larger particle size (2–4 μm). Cumulative effects are possible following repeated exposures (*51*).

Symptoms are both time- and dose-dependent (*52*). Mild incapacitation with some hallucination occurs at about 90 mg.min/m^3 (the i.v. equivalent dose is 4.60 μg/kg), severe incapacitation with marked hallucinations at 135 mg.min/m^3 (the i.v. equivalent dose is 6.16 μg/kg).

Based on data from animal studies and comparisons with fatalities due to atropine, the human median lethal dose is estimated to be in the range 0.5–3 mg/kg or 35–225 mg for a 70-kg individual.

Latency period from exposure to symptoms, and recovery time
Onset of symptoms is fairly rapid, regardless of the route of administration. In general, at milder incapacitating doses, symptoms abate within 48 hours. At serious incapacitating doses, delirium usually subsides within 72 hours, with recovery complete by 120 hours. Recovery is invariably gradual, simpler abilities returning initially; those requiring more complex integration (including judgement, social awareness and creative ideas) are restored last (*51*).

Main clinical symptoms
The toxicity of BZ, which is more potent than atropine and has a longer duration of action, is largely attributable to its anticholinergic properties. Signs and symptoms of exposure include increased heart rate and blood pressure; dry skin and mouth;

mydriasis; blurred vision; ataxia; disorientation and confusion leading to stupor. At lower exposures, subjects may be noticeably slower in action, less alert, and sleepy. As dosages increase, symptoms intensify — motor coordination deteriorates; confusion, apprehension and restlessness increase; and subjects lose contact with reality, becoming stuporose.

Following incapacitating doses of BZ, signs and symptoms appear in phases, as follows:

1–4 hours: restlessness, involuntary movements, ataxia, dizziness, nausea, vomiting, dry mouth, flushed skin, blurred vision, dilated pupils, confusion and sedation progressing to stupor.

4–12 hours: stuporose, even semiconscious, inability to respond to environmental stimuli, hallucinations.

12–96 hours: random unpredictable behaviour; increasing activity as subjects return to normal; hallucinations may dominate awareness. Real objects and individuals may be generally ignored or ludicrously interpreted. The hallucinations may be benign, entertaining or terrifying.

BZ inhibits secretory activity in the glandular cells concerned with digestion. Saliva is thick, tenacious and scanty, with dry mouth and marked pharyngeal discomfort. Swallowing can be painful, with speech reduced to a whisper. Breath has a foul odour and food and fluids may be refused for more than 24 hours. Urination may be difficult or impossible for up to 16 hours following exposure and frequent attempts to urinate may result (*51*).

In common with atropine, BZ inhibits sweating, and exposure to the chemical in hot, dry climates may induce heat-stroke. Some deaths and symptoms said to be consistent with exposure to an atropine-like chemical warfare agent and with severe heat stress have been reported (*53*), but it has also been claimed that the symptoms are more consistent with exposure to smoke from white phosphorus (*54*).

Long-term health implications
Evidence collected and reviewed from studies on volunteers exposed to BZ, from deliberate experimentation with the chemical, and from patients receiving repeat doses of atropine suggest that long-term effects are unlikely. There are limited mortality data on subjects following exposure to BZ in test situations. Data on mutagenicity are also limited and do not enable any conclusion to be reached. No carcinogenicity data are available (*52*, *55*).

Detection
Laboratory confirmation (and in mobile field laboratories) is by GC–MS. HPLC can also be used.

Principles of medical management
Patients should be removed from the source of exposure. Rapid triage should be conducted in the following order:

1. Haemorrhage and other surgical emergencies.
2. Coma.
3. Stupor.
4. Ataxia.
5. Ambulatory.

Clothing and any equipment likely to be contaminated should be removed. Powder on clothing should be prevented from becoming airborne.

Prophylaxis/treatment
Heat stroke should be avoided. Excessive clothing should be removed if the ambient temperature is above 25 °C. Bladder distension should be checked and hydration monitored. Dehydration is not likely to be a problem in the first 12 hours, but thereafter fluids should be administered *orally* only if the patient is able to drink unaided. Support should be provided and patients should be prevented from injuring themselves.

Physostigmine is the drug treatment of choice; however, in comatose, stuporose and ataxic patients it is of limited effectiveness earlier than 4 hours after BZ exposure. Physostigmine salicylate (1 mg per 20 kg, or 1 mg per 40 lb) i.v. should be given, but if the response is not satisfactory (fall in heart rate, mental clearing), a second, identical dose should be given. Thereafter, patients should be maintained on oral doses of 2–5 mg every 1–2 hours, as necessary. Solutions of the drug — which are bitter — should be added to a more palatable beverage. The frequency of treatment and the dosage should be reduced over 2–4 days.

With effective treatment, the supine heart rate will be 70–80 beats per minute and accompanied by clearer mental function. Treatment should be under the control of a physician. If no doctor is available, oral doses of physostigmine (1 mg per 10 kg) every 2 hours will provide partial control with safety. Both the frequency of treatment and the dose should be reduced 2–4 days after exposure.

Physostigmine is a toxic drug and care is needed to avoid overdosing, the signs of which are profuse sweating, clammy skin, abdominal cramps, vomiting, muscle twitching, tremors, weakness and other cholinergic symptoms. These are usually mild, and the short half-life of physostigmine (30 minutes) means that they are of short duration and rarely require additional treatment. If these symptoms do occur, the treatment should be delayed by 30 minutes and the dose of physostigmine reduced by one-third. Treatment should not be discontinued because the delirium of BZ may return rapidly (*56*).

Large overdoses of physostigmine may cause apnoea secondary to neuromuscular block. If apnoea does occur, mouth-to-mouth resuscitation should be given.

Barbiturates should not be used. Neostigmine and pilocarpine are ineffective antagonists of the effects of BZ on the CNS and should not be used instead of physostigmine.

If the number of patients is very large, mass confinement in a safe, cool area is the most important single measure.

Ambulatory patients should be observed for 8 hours and released if no more than mildly affected.

Stability/neutralization
Hydrolysis of BZ solutions is both time- and pH-dependent. Increasing pH will increase the rate of hydrolysis. An alkaline pH >13, achieved with 5% solutions of sodium hydroxide, will cause rapid hydrolysis.

To dispose of BZ, powder should be collected on a flammable material (e.g. paper or card) and incinerated in a well ventilated area. Alternatively, BZ should be dissolved in a suitable solvent, such as water. If the BZ powder dissolves, 5% sodium hydroxide should be added to neutralize the solution and diluted after 2 hours with additional water and discarded. If the BZ powder fails to dissolve in water, it is likely to be the free base, and should be dissolved in an organic solvent, e.g. chloroform or methylene chloride. BZ base is less soluble in acetone or alcohols, but will dissolve slowly in them. The mixture of BZ and the organic solvent should be incinerated.

BZ is likely to persist in the environment for some time. Data are not available on its half-life in or on soil.

Protection
A military-type gas mask will provide protection.

3.2 Harassing agents and other irritants

The harassing effects of the irritant disabling chemicals arise from the body's reflex responses to sensory irritation, and include lacrimation, sternutation, vomiting and pain (*57*). Any sensory irritant can provoke all these responses, and it is both the concentration and the tissue with which the agent comes in contact that will determine the response. The conjunctiva of the eyes is particularly sensitive to some irritants. If the predominant response is the secretion of tears, the irritant will be classed as a lacrimator. The inner surfaces of the nose or upper respiratory tract may be particularly sensitive towards other irritants, and such agents would be classed as sternutators. Gaseous irritants, or those dispersed as aerosol particles, penetrate to the deeper recesses of the respiratory tract. Inhalation of a high concentration of a sensory irritant may produce the same degree of damage to the lungs as the lethal lung irritant phosgene.

Skin irritants can also be used to harass, and some pruritogens and algogens (such as dichloroformoxime, also known as phosgene oxime) have been described as possible chemical warfare agents. The more severe skin irritants are also likely to cause damage to the lungs following inhalation which, as in the case of mustard gas, could disqualify them as disabling chemicals. Skin irritation, therefore, is unlikely to be a suitable property for a harassing agent, unless it is combined with other harassing effects, as occurs with some lacrimators and sternutators.

Just as police experience with irritants led to the battlefield use of disabling chemicals on the western front in the First World War in August 1914, so subsequent military experience with harassing agents promoted the use of these compounds for controlling civil disorder. Today, many police forces have access to the lacrimators CN and CS. A number of the military harassing agents are quite unsuited for use by the police, because of the risk of the total incapacitation of exposed individuals or even of death. The principal police requirement is either to incapacitate an individual temporarily in order to effect an arrest or, in the case of a riot, to force individuals out of a particular area.

An appropriate irritant for police use would be one with physical and toxicological properties ensuring that lethal exposures were extremely rare and harassing effects relatively mild. Agents currently employed by police forces around the globe include CS, CN and the active ingredient of red pepper, oleoresin capsicum. Deaths have been recorded following the use of all of these agents. However, apart from uses of CN in large concentrations that have been documented as the cause of lung damage, it is not possible to say whether the other two irritant agents caused death directly or merely contributed to it. A number of individuals died as a result of restraining techniques applied after they had been sprayed with irritant. Some restraining techniques will cause postural asphyxia, resulting in death (*58*, *59*). Where these techniques have been used on individuals who were also sprayed with an irritant, it has proved difficult to assess the contribution of the irritant in causing death. Many irritants employed by police forces are used in quantities significantly greater than those that would constitute an incapacitating dose.

3.2.1 *Adamsite*

Also known as 10-chloro-5,10-dihydrophenarsazine (CAS Registry Number 578-94-9), diphenylaminechlorarsine, phenarsazine chloride or DM, adamsite is a yellow-to-brown crystalline solid melting at 195 °C that was developed as a sternutator during the First World War. It is intensely irritating to the nose, throat and respiratory tract. Peripheral sensory nerves are affected, and eye, and to a lesser extent, skin irritation may occur. Lower dosages affect the upper respiratory tract; higher dosages cause deeper lung irritation.

Sources
Adamsite was once available commercially as a riot-control agent, in which role it is nowadays generally regarded as obsolete.

Exposure
Injury is normally through inhalation. Harassing effects of military significance occur at dosages of about 10 mg.min/m^3. Lethal dosages are estimated to be some 15 000 mg.min/m^3.

Latency period and recovery time
Symptoms are apparent 2–3 minutes after initial exposure. Recovery is usually complete in 1–2 hours if exposure is not prolonged.

Main clinical symptoms
Inhalation causes an initial irritant tickling sensation in the nose, followed by sneezing, and a flow of viscous mucus similar to that accompanying a bad cold. Irritation spreads down into the throat causing coughing and choking. Finally, air passages and lungs are also affected. Headache, especially in the forehead, increasing in intensity until almost unbearable, is accompanied by a feeling of pressure in the ears and pain in the jaws and teeth.

In parallel with these symptoms, there is oppressive pain in the chest, shortness of breath, nausea (followed shortly by violent retching and vomiting), unsteady gait, vertigo, weakness in the legs and all-over trembling. Mental depression may occur as symptoms progress. Very high dosages may damage the lungs. Deaths have been reported. Blistering on exposed arms, chest and neck has been reported in factory workers loading adamsite powder into munitions (*60*).

Detection
Adamsite has no odour. Symptoms are the first indication of exposure.

Rapid detection using GC–MS, the most specific technique, is now available. Many other methods for detecting arsenic in biological samples, including X-ray fluorescence and neutron activation, have been described (*61*).

Principles of medical management
The patient should be removed from the source of exposure. Clothing may be contaminated and should be removed with care to avoid spreading any powder.

Prophylaxis/treatment
Breathing may be relieved by inhaling low concentrations of chlorine, e.g. from a bottle of bleach. Dust particles in the eye and on the skin should be removed with copious amounts of water. Treatment, by and large, is symptomatic. If the inhaled dose is significant, the patient may require treatment for arsenic poisoning.

Decontamination/neutralization
Oxidation with solutions of hypochlorite (bleach), chloramine or potassium permanganate is effective.

Protection
A military-type gas mask provides protection.

3.2.2 *Agent CN*

CN is 2-chloroacetophenone (CAS Registry Number 532-27-4), a white crystalline solid melting at 59 °C and having an appreciable vapour pressure. It is a lacrimator that was under development at the end of the First World War and soon afterwards was widely used by police forces. It is intensely irritating to the eyes and the mucous membranes in the nose and upper respiratory tract. For police use, it may be disseminated as a pyrotechnically generated aerosol, as a dust cloud or, in solution, as

a liquid spray. In spray weapons, carrier/propellant solvents include trichlorofluoroethane, 1,1,1-trichloroethane and kerosene-type hydrocarbons (*62*).

Sources
CN is widely available commercially as a riot-control agent and in personal-protection devices.

Exposure
Irritation of the nose and respiratory tract occurs following inhalation, and irritation of the skin after direct contact.

Concentrations of 0.5 mg/m^3 will cause copious tears in under a minute. Military harassing dosages are in the region of 80 mg.min/m^3. Lethal dosages for humans are estimated to be between 7000 and 11 000 mg.min/m^3.

Latency period and recovery time
Symptoms occur almost instantaneously. Direct eye contact at low concentrations causes a copious flow of tears in less than a minute.

Symptoms persist for some 15–30 minutes after exposure ceases. Conjunctival irritation and injection may last 24 hours. Damaged skin may take 3–5 weeks to recover.

Main clinical symptoms
The toxicity of CN may be due to the alkylation and subsequent inhibition of sulfydryl-containing enzymes.

Stinging and burning of the eyes are usually the first symptoms, followed by similar effects on the nose and throat. Copious tears are produced, excess salivation and rhinorrhoea occur, as well as chest tightness, shortness of breath and gasping. Irritation is caused by contact with skin, and exposure to CN is associated with both primary and allergic contact dermatitis. Dermal contact with CN can cause itching, erythema, oedema, induration and necrosis. Necrotic eschars may occur some 5–6 days following contact. Skin recovery may take 3–5 weeks (*63*).

CN can have severe effects on the eyes including iridocycylitis, hypophyon, keratoconjunctivitis and stromal oedema. Permanent damage to the cornea of rabbits occurs with concentrations greater than 4%.

Lung damage occurs following the use of CN grenades in confined spaces. Injury to the lung may not be immediately apparent, and symptoms may be delayed for several days. Pulmonary oedema and bronchospasm have occurred following accidental, but prolonged exposure (*64*). Markedly oedematous lungs and intra-alveolar haemorrhage were observed at autopsy of an individual whose death was associated with inhalation of CN (*65*). Five deaths from lung damage have been reported following exposure to CN in confined spaces.

Long-term health implications

CN is embryotoxic and affects the nervous system of developing chick embryos. The effects are reversible with sulfhydryl compounds. Embryotoxicity occurrs at administered concentrations of 0.5–3 mmol, following exposures for 15–120 minutes. The effects of inhaling equivalent concentrations on humans are unknown. There is no evidence of malformations in humans attributable to CN exposure, and available evidence indicates that CN is neither a mutagen nor a carcinogen.

Detection
At low concentrations, CN smells like apple blossom. The odour threshold is 0.1–0.15 mg/m^3. Laboratory confirmation (and in mobile field vehicles) is by GC–MS. GC with thermal-conductivity or flame-ionization detectors may suffice if a well characterized method is used. HPLC methods are also available.

Principles of medical management
The patient should be removed from the source of exposure. Clothing and shoes may be contaminated, and should be removed with care to avoid any powder becoming airborne.

Prophylaxis/treatment
Any particles in the eye should be removed by flushing with copious amounts of water. For relief, the eyes can be washed with a weak solution of boric acid. The airways should be checked. Oxygen may be required if lung injury is evident. Contaminated skin should be washed with a solution of warm sodium carbonate solution. If this is not available, soap and water can be used; water alone is not nearly as effective, but may help if there is a plentiful supply. The affected area should be washed under running water for 20 minutes. Victims should be kept quiet and warm. Soothing lotions such as calamine can be used on injured skin (*29*, *63*).

Stability/neutralization
Data are insufficient to predict the biodegradation of CN in soil, a matrix in which it is likely to have moderate to high mobility.

CN in water may be broken down by UV light (photolysis), but the available data are insufficient to predict the rate of breakdown. Volatilization occurs slowly from water, and reported half-lives range from 13.3 to 159 days. Aquatic bioconcentration and absorption on sediment are minimal.

CN reacts with photochemically produced hydroxyl radicals and has a half-life of some 9.2 days in the vapour phase.

To dispose of CN, the chemical can either be wrapped in paper or some other flammable material, or dissolved in a flammable solvent, and burned in a suitable combustion chamber or well ventilated area. When heated, CN is degraded to hydrogen chloride.

Protection
A suitable respirator or military-type gas mask should be worn. Skin contact should be avoided. Protective clothing should be worn when clearing a large quantity of chemical arising from a spill.

3.2.3 *Agent CS*

CS is 2-chlorobenzalmalononitrile (CAS Registry Number 2698-41-1), also known as [(2-chlorophenyl)methylene]propanedinitrile, *o*-chlorobenzylidene malononitrile and ββ-dicyano-*o*-chlorostyrene. It is a white crystalline solid at ambient temperatures. It is a lacrimator that was initially developed to replace CN for police use but was subsequently also widely used on the battlefield. More rapid in action than CN, it is intensely irritating to the eyes and mucous membranes in the nose and upper respiratory tract. It is also a general skin irritant. For police use, it may be disseminated as a pyrotechnically generated aerosol, as a dust cloud, or, in solution, as a liquid spray. In spray weapons, the carrier solvents in use include methylene chloride, acetone and methyl isobutyl ketone, while the propellants include nitrogen, carbon dioxide and butane (*66*).

Sources
CS is widely available commercially as a riot-control agent.

Exposure
Irritation of the nose, throat and upper respiratory tract occur following inhalation, and of the skin through direct contact. Direct eye contact at low concentrations causes intense eye irritation and copious tears.

Eye and respiratory tract irritation is just detectable in 50% of people after 1-minute exposures to 0.004 and 0.023 mg/m^3 respectively. Harassment is marked at concentrations of 4 mg/m^3, with the eyes and respiratory tract affected almost immediately (*62*). As a peripheral sensory irritant, CS is about 10 times more potent than CN. Estimates of the human median lethal dosage, based on extrapolation from animal data, are uncertain and range from 25 000 to 150 000 $mg.min/m^3$. The particle size and method of delivery affect toxicity to the lung. Lethal concentrations cause lung damage, leading either to asphyxia and circulatory failure or to bronchopneumonia secondary to respiratory tract damage.

Latency period and recovery time
Eye and respiratory tract symptoms occur very rapidly at harassing concentrations of 4 mg/m^3. Recovery is usually complete 30 minutes after exposure ceases, but some signs may persist for longer. The usual times for recovery from particular effects are approximately as follows: visual acuity (a few minutes); chest discomfort (5 minutes); coughing and breathing difficulties (10 minutes); lacrimation (up to 15 minutes); salivation (15 minutes); skin sensations (15 minutes); conjunctival injection and subjective sensation of eye irritancy (25–30 minutes); erythema of eyelid margins (1 hour) (*62*).

Solutions of CS cause skin irritation, often as a two-phase response, with an initial erythema occurring within a few minutes and persisting for about an hour, followed some 2 hours later by a delayed erythema which persists for 24–72 hours. However, the onset of the delayed erythema may be as much as 12 hours–3 days after exposure,

with vesicles, blisters and crusts appearing on the skin (*67*). Recovery of the skin from this more serious damage may take weeks.

Main clinical symptoms
Stinging and burning of the eyes, lacrimation, rhinorrhoea, salivation, blepharospasm, conjunctival injection, sneezing and coughing develop rapidly at harassing concentrations. The chest may feel sore and tight, and some individuals may voluntarily hold their breath. Exposed skin, particularly in moist areas, begins to sting and burn after a few minutes, and erythema may follow. Some individuals may feel nauseous and vomit.

When the CS is delivered in a carrier solvent, exposure to the latter may sometimes further complicate the clinical picture. More CS is likely to be deposited on the skin and in the eyes by this procedure and both eye and skin irritation are more persistent (*63*, *67*).

Apprehension is common, and exposure to CS aerosols may cause a transient increase in both blood pressure and heart rate (*68*).

Eye damage, other than temporary conjunctival injection, is unlikely.

CS exposure is associated with both primary and allergic contact dermatitis, while reactive airways dysfunction syndrome (RADS) is a risk following exposure to high concentrations (*69*). Asthmatic symptoms may occur in susceptible individuals. Chronic bronchitics may suffer from a superimposed acute bronchitis and bronchopneumonia.

Authenticated deaths from CS have not been recorded. Deaths following the use of CS have occurred in police custody, and the role of CS in either causing or contributing such deaths is a cause of concern. High concentrations of CS in confined spaces over a prolonged period would be necessary to achieve lethal dosages. Under these conditions, lung damage could occur, leading to asphyxia and circulatory failure.

CS is an alkylating agent with cyanogenic potential. It undergoes stepwise metabolism to thiocyanate, some of which is then metabolized to cyanide. Any lethal effects of the agent would be mediated by both the alkylating properties and the cyanogenic potential. At harassing concentrations, however, cyanide production would be exceedingly small and of no clinical importance.

Long-term health implications
CS is mutagenic in some in vitro systems. However, it has not been demonstrated to cause mutations in vivo following administration to test animals. No evidence exists that CS is carcinogenic, and 2-year studies in rats and mice provided no evidence of carcinogenicity. Available evidence also indicates that CS is neither embryo-lethal nor teratogenic.

Detection

Symptoms are the first indication of exposure because of the low vapour pressure. Laboratory confirmation (also in mobile field laboratories) is by GC–MS. GC and HPLC methods are also available for CS and its metabolites (*61*).

Principles of medical management

The patient should be removed from the source of exposure. Clothing and shoes may be contaminated and should be removed carefully to avoid any powder becoming airborne. CS delivered in a solvent spray may become airborne after evaporation of the solvent and abrasion of the CS particles.

Prophylaxis/treatment

Treatment will depend on the way CS is delivered. If a fine powder is dispersed, it is preferable to keep it dry and blow as much of it as possible off the individual by using, for example, a hair dryer.

Spray delivery with a solvent will result in exposure to both CS and the solvent. Irrigation of affected areas with tepid water for at least 15 minutes is then advisable. Any particles deposited in the eye after evaporation of the solvent should be washed out by using copious amounts of tepid water for 15 minutes or more. Brief contact with water hydrolyses CS and may exacerbate burning symptoms. Soap and water can be used to wash the skin, but should be followed by irrigation with tepid water for 15 minutes. CS will dissolve rapidly in a solution of sodium metabisulfite, and such solutions can be used to remove solid particles of the irritant. Sodium metabisulfite solutions will release sulfur dioxide, which may be a hazard for asthmatics (*70*).

Saline or weak solutions of boric acid may relieve eye symptoms, and soothing lotions such as calamine can be used on injured skin. Wet dressings, which allow evaporation to take place (i.e. are not plastic-backed), may soothe skin. Dressings should be changed every 2–3 hours (*29*). Any skin infections should be treated with antibiotics. Airways should be checked and patients reassured.

Stability in environment/decontamination/neutralization

Formulations of CS are available that increase its persistence in the environment. Two hydrophobic anti-agglomerative powder formulations, CS1 and CS2, have been developed for explosive burst or fogging machines. CS1 contains 5% hydrophobic silica aerogel and persists for some 2 weeks under normal weather conditions. CS2, a siliconized form of CS1, has greater weather resistance, and may remain active for up to 48 days. Because of their persistence, these two forms of CS are likely to be used only in a military context (*62*).

CS powder used for riot control and dust derived from it can settle on the ground and remain active for 5 days. Traces of CS may persist for longer than this.

The data available are insufficient for any estimate of biodegradation in soil to be possible. Leaching can occur, but if CS is dissolved in water, hydrolysis is rapid and the agent will be degraded before leaching takes place.

Particle size and surface area affect the rate of dissolution in water, and CS can float and travel considerable distances before it dissolves. Its half-life in seawater is 281.7 minutes and 14.5 minutes at 0 °C and 25 °C, respectively.

At 25 °C, CS has an atmospheric half-life of some 4.9 days.

When heated, CS produces hydrogen chloride, nitrogen oxides and cyanide.

For disposal, particles should be swept on to a flammable material (e.g. paper or card) or dissolved in an organic solvent (such as alcohol) before burning in a suitable combustion chamber or in a well ventilated area. Spills can be decontaminated by washing with 5% sodium hydroxide solution in 1:1 ethyl alcohol (or isopropyl alcohol)/water mixture, leaving for 20 minutes and flushing with water.

Protection
A suitable respirator with a charcoal filter or a military-type gas mask should be worn. Protective clothing may be necessary to avoid skin contact when sweeping spills.

3.2.4 *Agent CR*

CR is dibenz-(b,f)-1:4-oxazepine (CAS Registry Number 257-07-8)**,** a pale yellow solid first characterized in the early 1960s. It is a sensory irritant some six times more powerful than CS. It is intensely irritating to the eyes and mucous membranes in the nose and upper respiratory tract. Application in liquid solution produces intense irritation of the skin, but the effects are less persistent than those produced by CS or CN. It may be disseminated as a pyrotechnically generated aerosol or as a liquid spray (*62*). Spray formulations of CR in a 0.1–1% solution in either propylene glycol and water or propylene glycol alone have been approved for riot-control purposes in the United States (*71*).

Sources
CR is available to internal security forces in a number of countries.

Exposure
Direct eye contact at low concentrations causes intense discomfort and pain and copious tears. The mouth, nose, throat and respiratory tract are irritated following inhalation, and direct contact will cause stinging, burning and occasional erythema of the skin.

Eye and respiratory tract irritation are detectable in 50% of people within 1 minite of exposure to concentrations of 0.004 and 0.002 mg/m^3. Harassment is marked at concentrations of 0.7 mg/m^3 (for aerosol), with effects on the eye and respiratory tract likely to be intolerable. CR has a very low mammalian toxicity, much lower than those of CS and CN. Based on animal data, the estimated acute lethal dosage for pyrotechnically generated CR in humans would be in excess of 100 000 mg.min/m^3 (*62*). Pyrotechnically generated CR is more toxic than pure (thermally generated) aerosols of the irritant because of the presence of pyrotechnic decomposition products.

Latency period and recovery time
Respiratory tract and eye irritation occur rapidly at harassing concentrations of 0.7 mg/m^3 or above. The principal effects of CR on the eyes and skin are likely to last less than 30 minutes, but some reddening of the eye may persist for hours. Pain and erythema of the skin occur within minutes of contamination. Although the pain usually subsides within 30 minutes, it will occasionally recur every time the skin is washed. Chest discomfort and breathing are likely to return to normal within about 15–30 minutes, as with CS.

The effects of CR on the eye are usually immediate but transitory. Single or multiple applications of CR either as a solid or in a 1 or 5% solution in propylene glycol have been tested on the eyes of rabbits. Solid CR caused only minor lacrimation and irritation of the conjunctivae for 1 hour. After single applications, CR in solution caused mild to moderate inflammatory effects for a few days. At higher concentrations (5% and 10%), a similar duration of effect was observed. After repeat applications over a number of weeks, the effect was a moderate transient conjunctivitis. Solutions of higher concentration (10%) cause detectable keratitis usually of only a few days duration. In humans, a rise in intraocular pressure of short duration is usually seen during the acute phase and may be an additional risk factor for the over-40s.

Solutions of CR (0.001–0.0025% w/v) have been applied as whole-body liquid drenches to the skin of volunteers. The eyes were immediately affected, with skin irritation starting around the eyes about a minute later and then at other sites. The degree of pain and erythema that occurred was related to the thickness of the stratum corneum, with the particularly sensitive areas being the face, back of the neck and trunk, and external genitalia (*68*).

Main clinical symptoms
Stinging and burning of the eyes, lacrimation, blepharospasm, conjunctival injection, rhinorrhoea, salivation, sneezing and coughing occur rapidly at harassing concentrations. Individuals may complain of difficulty in opening the eyelids and of an unpleasant taste or burning sensation in the mouth and on the skin. There may also be complaints of difficulty in breathing. On examination, the skin will show well demarcated, moderate to marked erythema. Blood pressure may be increased but usually returns to normal within 30 minutes. The inability to see clearly and the severe irritation may cause some subjects to develop anxiety, and this may be the main presenting complaint in some cases (*72*).

Subjects presenting more than 30 minutes after being splashed may complain of a "gritty" sensation in the eyes and of a mild burning of the skin. Examination may reveal residual conjunctival injection and erythema of the eyelids and contaminated skin.

Long-term health implications
There is no evidence that CR is teratogenic, mutagenic or carcinogenic. Embryo-lethal effects have been seen following intravenous administration; these may have been due to the precipitation of CR from saturated solution on injection (*73*).

Detection

Symptoms are the first indication of exposure. Laboratory confirmation (and in mobile field laboratories) is by GC–MS. In addition to GC, HPLC methods are also available for the separation of CR. Data on nuclear magnetic resonance and infrared spectra are well characterized and can be used for identification (*61*).

Principles of medical management
The patient should be removed from the source of exposure. Contaminated clothing should be removed with care by personnel wearing impermeable gloves and placed in suitable containers (e.g. disposable polyethylene bags). The skin should be decontaminated with soap and water. If the hair is contaminated, care should be taken to prevent any material from being washed into the eyes.

Prophylaxis/treatment
The patient should be reassured by stressing that the pain is temporary. Particles should be washed out of the eye with copious amounts of tepid water. Saline or weak boric acid solutions may relieve eye symptoms and can be used to irrigate the eyes. If pain in the eye persists, it may be relieved by instillation of 0.5% tetracaine hydrochloride, appropriate precautions being taken to avoid mechanical trauma. Acute burning sensations of the skin subside after about 10 minutes. Both skin and hair should be washed thoroughly with soap and water and only after washing, if necessary, should a soothing lotion such as calamine be applied to the skin. It is possible that CR will exacerbate the effects of psoriasis or eczema in some patients, and the normal treatment of these conditions should be used. Rhinorrhoea and excessive salivation are transient, and any symptoms in the mouth disappear rapidly. The mouth should be washed if necessary.

Stability/neutralization
Because of its stability, CR may persist in the environment for months. The dibenzoxazepines were stable for several hours when refluxed in concentrated hydrochloric acid and in 20% sodium hydroxide (*74*). Failure to hydrolyse dibenzoxazepines under these extreme acidic and alkaline conditions demonstrates significant stability. The ether linkage in the molecule has been broken by reduction with sodium and ethanol, but no practical decontaminant is available at present. CR is very toxic to aquatic life (*75*).

Protection
A suitable respirator with a charcoal filter or a military-style gas mask should be worn. Protective clothing may be necessary to avoid contact when cleaning spills.

3.2.5 *Agent OC*

OC is oleoresin capsicum, a natural oil of the chilli pepper, *Capsicum annuum* or *C. frutescens* (Solanaceae family) that is almost insoluble in water but soluble in such organic solvents as ether, alcohol or chloroform. The active principles of OC, typically constituting some 60–80% of the oil, are capsaicin, also known as *trans*-8-methyl-*N*-vanillyl-6-nonenamide (CAS Registry Number 8023-77-7), and dihydrocapsaicin, but at least 100 other chemicals are also present in OC. Capsaicin can also be synthesized. The substance was proposed for use as a harassing agent during the First World War,

but does not appear to have been used as a disabling chemical until long afterwards, in personal-protection devices. It is now quite widely used by police forces in the form of "pepper spray". Such sprays typically contain 1–10% of OC oil in a solvent/propellant. OC acts rapidly and is an intense irritant to the eyes, nose and respiratory tract. It is also a mild skin irritant. "Pepper spray" is a designation sometimes also used for compositions containing synthetic congeners of capsaicin, such as pelargonic acid vanillylamide (PAVA).

Sources
OC is isolated commercially from paprika and cayenne pepper, and is used as a flavouring agent in some foods. It also has medicinal applications and has been used for centuries for pain relief. It is now used following herpes zoster infections (post-herpetic neuralgia) and for psoriasis, diabetic neuropathy and a range of other conditions (*76*).

Exposure
Direct eye contact at low concentrations causes intense eye irritation and copious tears. Irritation of the nose, throat and upper respiratory tract occur following direct contact.

Incapacitating dosages in humans are not documented; but 50 mg/litre concentrations applied to the eyes of rats caused obvious pain and blepharospasm. Estimated oral lethal doses in humans range from 0.5 to 5g/kg (*77*).

Capsaicin acts on nociceptive afferent nerve fibres, and is thought to deplete Substance P, a neurotransmitter of pain. Topical application of capsaicin desensitizes an area of skin to chemical, thermal and mechanical stimuli in a dose–dependent manner.

Latency period and recovery time
Eye and respiratory tract symptoms occur almost immediately after spraying OC on the face. Severe pain and inflammation last from 45 minutes to several hours. Lingering effects usually disappear in 1–2 days. Deaths have been recorded following the use of OC sprays, but in the majority of cases, other factors such as the use of cocaine, or postural asphyxia (caused by restraining procedures) were considered to be the likely cause of death (*58*). Pepper spray is documented as contributing to only one death, that of an asthmatic (*78*).

Main clinical symptoms
The main symptoms are stinging and burning of the eyes, and lacrimation, and burning of the nose and mouth. Inhalation of aerosol will cause sneezing, rhinorrhoea, choking and gasping for breath. Erythema may be present on exposed skin. Bronchoconstriction may occur in subjects with obstructive lung disease.

Long-term health effects
There is some concern about neurotoxic effects, but these have not been documented in humans following topical application. There is equivocal evidence on mutagenicity, and both positive and negative results have been reported for different test systems. The evidence available is not sufficient to evaluate carcinogenicity, but it is unlikely

to be of real concern following a single exposure to a relatively low dose of capsaicin in a spray (*78*).

Detection in the laboratory
GC and HPLC procedures are available (*79*).

Principles of medical management
Patients should be removed from the source of exposure. Clothing may be contaminated and should be removed. Capsaicin is not volatile and presents no vapour hazard.

Prophylaxis/treatment
A jet of liquid will probably have been sprayed in the face. Irrigation of the eyes with water is the most common treatment described, but capsaicin is practically insoluble in water so that more effective procedures are required. Skin can also be washed with vegetable oils (*78*).

Patients should be reassured and bronchoconstriction treated, if present.

Stability in environment/decontamination/neutralization
As capsaicin is not volatile, the only risk is from direct contact. Capsaicin should be removed from contaminated clothing with an organic solvent and burned.

Protection
Eyes, nose and mouth should be protected with a military-type gas mask.

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