

## 3. BIOLOGICAL AND CHEMICAL AGENTS

Careful advance planning is essential if a Member State or other country is adequately to manage the threat or the consequences of deliberate releases of biological or chemical agents. A central consideration in such preparedness planning is that it is neither possible nor necessary to prepare specifically for attack by all possible biological and chemical agents. If a country is seeking to increase its preparedness to counter the effects of biological and chemical attacks, the targeting of its preparation and training on a limited but well chosen group of agents will provide the necessary capability to deal with a far wider range of possibilities. Knowledge of the general properties of this representative group of agents will enable certain measures to be taken against virtually any other agent. In addition to being impractical from a preparedness perspective, long and exhaustive lists of agents also give a misleading impression of the extent of possible threats. In this chapter, an approach to identifying agents of concern is described, followed by a discussion of methods of dissemination, routes of exposure, and general characteristics of biological and chemical weapons, from which conclusions are drawn to complete the threat assessment initiated in Chapter 2.

### 3.1 The representative group of agents

Biological and chemical weapons have been described as the “poor man’s atom bomb”, but this conveys a misleading impression of their ease of production and their utility. It is not enough for biological and chemical agents to be highly infective or highly toxic. In order to be selected for weaponization, a candidate agent should have characteristics that are capable of countervailing the technical limitations that would otherwise render the weapon carrying the agent unattractive to users, such as the technical limitations just described in Chapter 2. So the agent will need to be stable enough to resist degradation during handling and storage, and during the energy-transfer processes that will, in most scenarios, be involved in disseminating it on its target. Once disseminated, the agent must be capable of establishing field dosages

that are infective or toxic over a predictable area. It must also be relatively easy to produce from readily available precursor compounds or from naturally occurring or genetically modified microorganisms. Once produced and, depending on the agent, further processed and formulated, it must be filled into munitions or dissemination devices, or held ready for such filling, and be storable without undue risk to its possessor. If an agent is insufficiently stable in storage, certain expedients are available, such as, in the case of some chemicals, the use of “binary” munitions that are uploaded, not with toxic agent, but with separate containers of precursors, these being adapted to mix and generate the agent either just before or during weapon launch. For biological agents, a “warm” production base rather than a large stockpile has been relied upon in past offensive military programmes.

While many thousands of toxic chemicals and hundreds of pathogenic microorganisms have been investigated for their potential utility as military weapons, relatively few have been found capable of meeting military requirements of the kind just specified, and fewer still have found their way into weapons and actually been used. The task facing public health authorities of identifying a representative group of agents against which to prepare might therefore be thought relatively straightforward. However, the deliberate agent releases against which public health authorities would need to prepare might include attacks by non-state entities whose agent-selection principles could differ from the military ones. For example, accessibility, not overall aggressiveness and stability in storage, might be the dominant criterion in their choice of agent. Also, the types of impact sought could differ from those that direct military operations. In other words, the rank order in which public health authorities assess the different agent threats, e.g. reference (1), may not be the same as that of military authorities. In the present study, the representative group has been compiled by applying a progressively sharper focus to possible agents of concern: firstly, the broad treaty definitions of biological and chemical weapons; secondly, the lists of agents that have been negotiated to facilitate treaty implementation, or, in the case of the BWC, proposed therefor; thirdly, such authoritative information as is publicly available about which agents have been weaponized or stockpiled in recent times; fourthly, agents known to have been used as weapons; and

finally, considerations regarding non-state entities. This selection process is now described.

### *3.1.1 Scope of the international treaties*

The broadest catchment of agents of concern, and therefore the starting point for the selection process, is to be found in the treaties that outlaw possession of biological and chemical weapons. The intergovernmental negotiations that culminated in the BWC and then the CWC commenced while the first edition of the present report was being prepared. In 1969, in order to determine its scope, WHO relied on the concepts of toxicity and infectivity to distinguish chemical and biological weapons from other types of weapon. It defined chemical-warfare agents as including “all substances employed for their toxic effects on man, animals and plants”, and biological-warfare agents as those “that depend for their effects on multiplication within the target organism, and that are intended for use in war to cause disease or death in man, animals or plants”. The treaty negotiators had, however, to devise definitions that used a broader approach, since they were aiming to control technologies that were often dual-use in character, in other words that could be used both in warfare and for peaceful purposes. For example, the negotiators could not prohibit the production of the principal lethal gas of the First World War, phosgene, without at the same time denying feedstock to manufacturers of certain plastics and other useful products; nor could they outlaw the large-scale growth of pathogenic microorganisms without threatening vaccine production. There were many such examples, so the negotiators took the general purpose for which a biological or a chemical agent was intended as the criterion of whether activities involving that agent should or should not be subject to prohibition or control under the treaties. Such a general-purpose criterion is therefore to be found in those parts of both the BWC and the CWC where the scope of the treaty is defined. Thus, the prohibitions laid down in the two treaties extend to all biological agents and toxins, and to essentially all chemicals, unless they are intended for peaceful purposes, and unless their types and quantities are consistent with such purposes. In addition, the CWC uses the concept of toxicity, applying its general purpose criterion to “toxic chemicals” and “their precursors”, and

**defining both of these categories of chemical in broad terms. In contrast, the BWC does not seek to define the biological agents and toxins to which it applies. The actual language used in the two Conventions to define the weapons to which they apply is given in Box 3.1 below.**

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**Box 3.1    How biological and chemical weapons are defined in the BWC and the CWC**

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**Article I of the Biological Weapons Convention reads as follows:**

Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:

1. Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.
  2. Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.
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**Article II of the Chemical Weapons Convention includes the following:**

For the purposes of this Convention:

1. "Chemical Weapons" means the following, together or separately:
  - (a) Toxic chemicals and their precursors, except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes;
  - (b) Munitions and devices, specifically designed to cause death or other harm through the toxic properties of those toxic chemicals specified in subparagraph (a), which would be released as a result of the employment of such munitions and devices;
  - (c) Any equipment specifically designed for use directly in connection with the employment of munitions and devices specified in subparagraph (b).

2. "Toxic Chemical" means:

Any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, in munitions or elsewhere.

(For the purpose of implementing this Convention, toxic chemicals which have been identified for the application of verification measures are listed in Schedules contained in the Annex on Chemicals.)

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9. "Purposes Not Prohibited Under this Convention" means:

- (a) Industrial, agricultural, research, medical, pharmaceutical or other peaceful purposes;
  - (b) Protective purposes, namely those purposes directly related to protection against toxic chemicals and to protection against chemical weapons;
  - (c) Military purposes not connected with the use of chemical weapons and not dependent on the use of the toxic properties of chemicals as a method of warfare;
  - (d) Law enforcement including domestic riot control purposes.
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**In order to implement treaties of such wide-ranging scope effectively, lists of agents have been drawn up so as to focus the efforts of the implementers by providing transparency for the agents that all States Parties could agree had potential for use as chemical weapons. The CWC includes three such negotiated lists ("Schedules") in which selected toxic chemicals and precursors are "identified for the application of verification measures". These schedules are set out in the treaty's *Annex on Chemicals*, and list 29 specific chemicals and 14 families of chemicals. Some of the families are very large indeed, running into many millions of chemicals, most of which have, however, never actually been made or characterized. For example, the dialkyl alkylphosphonates that constitute only a small fraction of the chemicals in item 4 of Schedule 2 comprise 1 668 964 different chemicals (excluding stereoisomers), of which apparently only 118 have actually been synthesized (2). Even the family of alkyl alkylphosphonofluoridates, with which Schedule 1 opens, i.e. the sarin family of nerve gases, theoretically contains 3652 members. Large though these numbers are, the CWC makes it clear that its Schedules are not intended to be a definitive listing of all chemicals that constitute "risks to the object and purpose of this Convention", but simply to exemplify chemicals thought to pose**

a particular risk of being used in a manner contrary to its general-purpose criterion.

The BWC, which is a legal instrument much shorter and simpler than the CWC, contains no analogous schedules, but such lists have been developed for inclusion in the BWC Protocol were its negotiation to be completed. The purpose of these lists would again be to exemplify, but not to define, the scope of the general-purpose criterion. Several other authorities, including defence agencies, have compiled lists of biological agents judged most likely to be employed for hostile purposes. Some of these lists are shown in Table A3.1 in Annex 3, from which it may be seen just how much variation there can be in different agent assessments.

### *3.1.2 Historical experience*

Toxic and infective agents that were available in weaponized forms in the past to the armed forces of states are identified in official state papers now open to the scrutiny of historians. This historical record is not complete, however, because former possessor states have not yet made all of the relevant papers available, and even those that have done so have still withheld the papers of the last 20 or 30 years (the declarations received by the United Nations Special Commission on Iraq – UNSCOM – are an exception in that they include reference, albeit not yet entirely verified, to weaponization during the period 1987–1991). An extensive list of antipersonnel agents can nevertheless be compiled. That given in Table 3.1 covers the period since January 1946 and is taken from an archive of collected state papers, works of historical scholarship and other documentation at the University of Sussex.<sup>5</sup> It is limited to agents identified in state papers of the country concerned as having been stockpiled or having otherwise entered the process of weaponization. For convenience, Table 3.1 groups the agents into categories that are explained later in this chapter.

For some of the toxic chemicals included in Table 3.1, an indication of relative importance historically in possessor state programmes can be gained by considering the quantities of the different agents that have

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<sup>5</sup> The archive is the Sussex Harvard Information Bank, which is maintained at SPRU, University of Sussex, UK, by the Harvard Sussex Program on CBW Armament and Arms Limitation (see [www.sussex.ac.uk/spru/hsp](http://www.sussex.ac.uk/spru/hsp)).

been declared to OPCW as part of the obligatory declarations of chemical weapons required from States Parties to the CWC. These declared quantities are given in Table 3.2, which shows that an aggregate total of 69 863 tonnes of chemicals have been declared as chemical weapons to OPCW by its Member States. These declared stockpiles are subject to the monitoring provisions of the CWC, and their destruction under agreed protocols is observed by OPCW officials. By 31 August 2003, a total of 7837 tonnes had been destroyed.

The information on the actual use of toxic and infective agents for hostile purposes may be even less complete than that on weaponization or stockpiling, not least because of the role of these agents in clandestine warfare, on which official records are often sparse. Moreover, there have been occasions when it has been reported that chemical and biological weapons have been used when in fact they were not, the reports originating either in misperception or other error, or in the intention to deceive. Table 3.3 summarizes the record of antipersonnel use, taken from the same archive as that used for Table 3.1. Its entries are restricted to those instances since 1918 in which the fact of use can be regarded as indisputable, and in which the toxic or infective agents employed have been identified. The use of anti-plant or anti-animal agents is not included. Table 3.3 includes in its last three entries the use of toxic or infective antipersonnel agents by non-state entities – acts of terrorism on which the historical record is still more sparse.

Tables 3.1, 3.2 and 3.3 list 40 different biological and chemical agents, which is a number considerably smaller than the number of agents described in the literature on biological and chemical warfare. Not all of the 40 are readily accessible only to state forces, for among them are widely used industrial chemicals. For inclusion within the representative group of agents, some may be disregarded on grounds of close similarity to one another. It seems necessary to add only four further agents. These are: variola major, i.e. smallpox virus; the fungal agent that causes coccidioidomycosis; perfluoroisobutene, a toxic agent now produced as a by-product in the chemical industry in tens of thousands of tonnes per year; and the chemical psychotomimetic agent lysergide, also known as LSD. Although none of these four additional agents is listed in Table 3.1, all four are known to have been studied for possible

**weaponization including, in some cases, actual field trials as well as laboratory study.**

**Described in Annexes 1, 2 and 3 are 26 of the 44 agents, which thus include those from among which a public health authority may reasonably select its representative group of agents.**

Table 3.1 **Toxic and infective antipersonnel agents stockpiled or otherwise weaponized for state forces since 1946 according to official documents of their possessor states**

**Tear gases, other sensory irritants, and other disabling chemicals**

10-chloro-5,10-dihydrophenarsazine (adamsite, or DM)

$\omega$ -chloroacetophenone (CN)

$\alpha$ -bromophenylacetonitrile (Iarmine, BBC or CA)

2-chlorobenzalmalononitrile (CS)

dibenzoxazepine (CR)

oleoresin capsicum (OC)

3-quinuclidinyl benzilate (BZ)

**Choking agents (lung irritants)**

phosgene

chloropicrin

**Blood gases**

hydrogen cyanide

**Vesicants (blister gases)**

bis(2-chloroethyl) sulfide (mustard gas)

2-chlorovinylchloroarsine (lewisite)

bis(2-chloroethylthioethyl) ether (agent T)

tris(2-chloroethyl)amine (a nitrogen mustard)

**Nerve gases**

ethyl *N,N*-dimethylphosphoramidocyanidate (tabun, or GA)

*O*-isopropyl methylphosphonofluoridate (sarin, or GB)

*O*-1,2,2-trimethylpropyl methylphosphonofluoridate (soman, or GD)

*O*-cyclohexyl methylphosphonofluoridate (cyclosarin, or GF)

*O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (VX)

*O*-isobutyl *S*-2-diethylaminoethyl methylphosphonothiolate (Vx)

**Toxins<sup>a</sup>**

ricin

saxitoxin

*Clostridium botulinum* toxin

staphylococcal enterotoxin

aflatoxin

**Bacteria and rickettsiae**

*Bacillus anthracis*

*Francisella tularensis*

*Brucella suis*

*Burkholderia mallei*

*Burkholderia pseudomallei*

*Yersinia pestis*

*Rickettsia prowazeki*

*Coxiella burnetii*

**Viruses**

Venezuelan equine encephalitis virus

<sup>a</sup> In addition to those already listed, namely OC and hydrogen cyanide.

Table 3.2 Aggregate quantities of chemical agents declared to the OPCW by its Member States, as of 31 December 2002

Chemical agent	Total declared (tonnes) <sup>a</sup>		
<b>Category 1 chemical weapons<sup>b</sup></b>			
Agent Vx	15 558		
Agent VX	4 032		
Difluor (precursor DF) <sup>c</sup>	444		
EDMP (precursor QL) <sup>d</sup>	46		
Isopropanol/isopropylamine (precursor OPA) <sup>e</sup>	731		
Lewisite	6 745		
Mustard gas <sup>f</sup>	13 839		
Mustard/lewisite mixtures	345		
Runcol (agent HT) <sup>g</sup>	3 536		
Sarin (agent GB)	15 048		
Soman (agent GD)	9 175		
Tabun (agent GA)	2		
Unknown	5		
<b>Category 2 chemical weapons<sup>b</sup></b>			
Chloroethanol	302		
Phosgene	11		
Thiodiglycol	51		
<b>Chemicals declared as “riot control agents”<sup>h</sup></b>			
Adamsite	Agent CN	Agent CS	Agent CR
Chloropicrin	Agent OC	OC/CS mixture	MPA [ <i>sic</i> ]
Ethyl bromoacetate	Pepperspray [ <i>sic</i> ]	Pelargonic acid vanillylamide	

<sup>a</sup> Based on figures from OPCW annual report for 2002 (3), rounded to the nearest tonne. Excludes chemicals declared in quantities of less than one tonne. One such chemical was the nerve-gas *O*-ethyl *S*-2-dimethylaminoethyl methylphosphonothiolate, also known as médémo or EA 1699.

<sup>b</sup> The CWC Verification Annex, in Part IV(A) para. 16, defines Category 1 as “chemical weapons on the basis of Schedule 1 chemicals and their parts and components”. See Table 3.1 for their chemical identities.

<sup>c</sup> Methylphosphonyl difluoride (a binary nerve-gas component).

<sup>d</sup> Ethyl 2-diisopropylaminoethyl methylphosphonite (a binary nerve-gas component).

<sup>e</sup> A mixture of 72% isopropanol and 28% isopropylamine (a binary nerve-gas component).

<sup>f</sup> Including “mustard gas in oil product”.

<sup>g</sup> A reaction product containing about 60% of mustard gas and 40% of agent T.

<sup>h</sup> “Chemical weapons on the basis of all other chemicals and their parts and components.” The CWC goes on to define Category 3 chemical weapons as comprising “unfilled munitions and devices, and equipment specifically designed for use directly in connection with employment of chemical weapons”.

<sup>i</sup> For chemicals declared as “riot control agents”, the CWC requires disclosure of their chemical identity but not the quantities in which they are held.

Table 3.3 Antipersonnel toxic and infective agents whose hostile use since 1918 has been verified

Period	Agent	Location of use
1919	adamsite diphenylchloroarsine (a sensory irritant) mustard gas	Russia
1923–1926	bromomethyl ethyl ketone (a tear gas) chloropicrin mustard gas	Morocco
1935–1940	chlorine (a choking agent) $\omega$ -chloroacetophenone diphenylchlorarsine mustard gas phenyldichlorarsine (a vesicant) phosgene	Abyssinia
1937–1945	$\omega$ -chloroacetophenone diphenylcyanoarsine (a sensory irritant) hydrogen cyanide lewisite mustard gas phosgene <i>Yersinia pestis</i>	Manchuria
1963–1967	$\omega$ -chloroacetophenone mustard gas phosgene	Yemen
1965–1975	2-chlorobenzalmalononitrile	Viet Nam
1982–1988	2-chlorobenzalmalononitrile mustard gas sarin tabun	Iraq Islamic Republic of Iran
1984	<i>Salmonella enteritidis</i> serotype <i>typhimurium</i>	United States
1994–1995	sarin	Japan
2001	<i>Bacillus anthracis</i>	United States

Source: Documents and materials held in the Sussex Harvard Information Bank at SPRU – Science and Technology Policy Research, University of Sussex, United Kingdom.

## 3.2 Dissemination of biological and chemical agents

In any release of a chemical or biological agent, the nature and degree of hazard will depend on a multitude of factors, including the agent and the amount released, the method by which the agent is disseminated, factors that influence its toxicity, infectivity or virulence both during and after its release, its movement and dilution in the atmosphere, and the state of protection and susceptibility of those exposed. Two different types of general hazard are usually distinguished, namely inhalation hazard and contact hazard, with different characteristic implications for protection (see Chapter 4). A brief summary is given here of the methods of airborne dissemination of biological and chemical agents that may create an inhalation or contact hazard to unprotected persons. Considered elsewhere in this study are certain other methods of agent dissemination, including dissemination through drinking water and food. For biological agents there is also the possibility of using arthropod vectors.

The methods of airborne dissemination that may be used depend on the physical and chemical properties of the material to be dispersed, including those that might cause the decomposition or inactivation of chemicals or toxins or, for infective agents, the loss of viability or more subtle changes that primarily affect only virulence.

For chemical agents, an inhalation hazard may be created by the dissemination of the agent as a vapour, as liquid or solid particles sufficiently small to be inhalable, as a spray that evaporates to form a vapour while still airborne, or as a spill or spray that is deposited on surfaces and subsequently evaporates to form a vapour. For some agents, vapours or inhalable particles may also present a hazard to sensitive mucous membranes, especially those of the conjunctiva. For chemical agents able to act percutaneously, a contact hazard may be created by sprays or spills of less volatile agents deposited directly on people or on surfaces with which people are likely to come into contact. A chemical agent may be disseminated mechanically by spraying or rupturing a container, by using explosives, or by a thermal process in which a pyrotechnic composition is used as the source of heat. Pyrotechnic dissemination is effective only for heat-resistant

and non-combustible agents, which may evaporate initially and then condense as a suspension in air of inhalable particles, creating principally a respiratory or conjunctival hazard.

For infective agents, the principal hazard to people will be from inhalation. This may be so even for agents for which this is not the natural route of infection. For many infective agents, the risk is greatest if the agent reaches the target population in the form of particles within the narrow aerodynamic size range where particles are small enough to penetrate to the alveoli in the depths of the lungs but not so small that most of them fail to be deposited and instead are mostly exhaled. Contact with an infective agent and its entry into the body via a lesion or via mucous membranes may also present a risk, although generally less than that from inhalation. Infective agents may be disseminated as inhalable particles by dispersal of presized powder, by explosives or by sprayers or other generators specially designed to produce particles in the inhalable size range.

Small particles may have such low gravitational settling velocities that the movement in the atmosphere of a cloud of such particles is like that of a vapour cloud. A particulate cloud of this type is a colloidal suspension of matter in air, and is known as an aerosol. For both vapours and aerosols, the rate of deposition depends not on gravity but rather on chemical and physical forces that might bind the molecules or particles to the specific surfaces with which they come into contact, thereby removing them from the cloud at a rate that also depends on surface roughness and on meteorological factors. It is the effective aerodynamic diameter that is the proper measure of size in regard to the settling and impaction propensities of small particles. Only for solid spheres of unit density does the effective aerodynamic diameter reduce to actual diameter. This distinction may be important for lyophilized materials that are largely hollow or for chemical agents that are very dense. Wind and other mechanical disturbances may resuspend deposited particles, but the amount resuspended is likely to be small and even that may be bound to soil or other particles of larger diameter. In consequence, exposures to inhalable particles resulting from resuspension of particles deposited from an aerosol will generally be much lower than those caused by the initial cloud.

As a particulate or vapour cloud is carried down-wind, eddy currents in the atmosphere cause it to spread both horizontally and vertically (up to the top of the atmospheric mixing layer, if such a layer is present) at a rate that depends strongly on the degree of atmospheric turbulence, resulting in lower dosages at greater down-wind and cross-wind distances from the source. Nevertheless, if the atmosphere is relatively stable, and depending on the nature and amount of the agent, dosages may reach hazardous levels even many kilometres down-wind of the source.

### 3.3 Routes of exposure

#### 3.3.1 *Respiratory system*

The principal hazard from agent vapours and aerosols is respiratory, although certain chemical agents, notably the mustards and sensory irritants, also pose a particular hazard to the conjunctiva.

The region of the respiratory system where the inhaled vapour of a chemical agent is adsorbed and the efficiency of its adsorption depend on the solubility properties of the agent. Vapours of water-soluble agents are largely adsorbed in the nasal passages and the upper regions of the respiratory system. Water-insoluble vapours are able to penetrate more deeply and may be adsorbed in the most distal part of the respiratory system – the alveolar spaces. For an aerosol of a non-volatile agent or for an agent adsorbed to a non-volatile carrier material, the site of deposition will depend on the size and density of the aerosol particles, as discussed below for biological agents.

Some agents, including mustard, phosgene and chlorine, damage lung tissues at the site of adsorption, while others, such as the nerve agents, penetrate respiratory tissues and are carried through the bloodstream to act on specific target receptors, as in the peripheral or central nervous system.

For chemical agents that are not significantly detoxified during the period of exposure, the severity of hazard depends on the total amount

inhaled. For some chemicals, however, notably hydrogen cyanide, significant detoxification occurs in the body within minutes, so that inhalation of a given amount within a short time may cause severe intoxication or death while inhalation of the same amount over a longer time would not. Most of the chemical agents listed in Table 3.2, however, including mustard and the nerve agents, are essentially cumulative in their toxic effects, except perhaps for exposures extending over many hours.

The principal hazard to persons exposed to a passing cloud of a biological aerosol would also be respiratory. This is because the amount of aerosol deposited in the respiratory system would be greater than that deposited elsewhere on the body and because the respiratory system, although provided with impressive natural defence mechanisms, is nevertheless vulnerable to infection by the agents of concern. It is also the case that, for many agents of concern, infection via the inhalatory route generally leads to more severe disease than does cutaneous infection. Nevertheless, if an agent finds its way to a lesion, cutaneous infection may result from aerosol particles deposited on bodily surfaces or on surfaces with which the person comes in contact.

The region of the respiratory system where inhaled particles are deposited depends on their aerodynamic diameter. As an approximation, the particles in a biological agent aerosol are taken to have unit density and spherical shape. Such particles with diameter around 10  $\mu\text{m}$  and larger are almost entirely deposited by inertial impaction on the fimbriae of the nose, in the nasal cavities and in the upper thoracic airways. After deposition, they are transported to the nose or to the back of the throat by mucociliary action, to be expelled in nasal secretions or to be swallowed or expelled by coughing, spitting or sneezing. Such clearance protects the lungs from particulates including infective agents deposited in the respiratory airways. Additional protection against infective agents results from the action of antimicrobial substances present in mucus and from the action of phagocytic cells. Some infective agents, however, including the viruses of influenza and smallpox, have special adaptations that enable them to infect the oropharyngeal and respiratory mucosa. Infection by such agents may therefore result, not only from inhalation of contam-

inated particles, but also by hand–mouth and hand–nostril transfer from contaminated materials and surfaces.

Smaller particles, in the range 1–5  $\mu\text{m}$  in diameter, may also be trapped in the nasal passages but a substantial percentage of them will escape inertial impaction and pass beyond the respiratory airways to reach the alveoli, where they may deposit by gravitational sedimentation. It is here, in the approximately 300 million alveoli with a total surface area of some 140  $\text{m}^2$ , that most biological agents of concern, if disseminated as aerosols sufficiently fine to reach the alveoli, may initiate infection. Because of their lower gravitational settling velocities, inhaled particles with diameters below 1  $\mu\text{m}$  are not likely to deposit by sedimentation but, if not simply exhaled, may nevertheless deposit on alveolar surfaces, owing to Brownian motion (4).

Consistent with their gas-exchanging function, the alveoli lack ciliated epithelium and therefore lie beyond the mucociliary surface of the respiratory airways. Instead, alveolar clearance of insoluble particles is mainly achieved by mobile phagocytic cells, the alveolar macrophages, or by polymorphonuclear leukocytes which are subsequently engulfed by alveolar macrophages. Macrophages that have engulfed deposited particles may remain permanently in the alveolar connective tissue or, by processes that are poorly understood, reach the respiratory airways and be removed from the lungs by mucociliary transport. Particles may also be transported by macrophages or pass as free particles to regional lymph nodes, to be retained there or to enter the lymphatic drainage, passing through the thoracic duct into the bloodstream.

Alveolar clearance has half-times ranging from hours to many days or longer, depending on the nature of the particle. Most microorganisms and viruses engulfed by macrophages are inactivated and digested. Some microorganisms, however, are endowed with features that enable them to resist phagocytosis or to survive or multiply within macrophages. Spores of *B. anthracis*, for example, are able to germinate in macrophages, which may transport bacteria to regional lymph nodes where proliferation and passage of bacteria into the bloodstream can initiate systemic infection.

### 3.3.2 *Skin*

Several chemical agents, such as the liquid agent VX, are able to penetrate the skin and cause systemic effects. Others, such as the blister agent mustard, either as a liquid or as vapour, cause more local effects, and, in addition, may render the underlying tissues vulnerable to infection. As a general rule, the thinner, more vascular, and moister the skin, the more prone it is to attack and penetration by such agents. High relative humidity promotes penetration. As penetration into and through the skin is not immediate, removal by washing, wiping or decontamination, if accomplished within minutes after exposure, can greatly reduce the toxic effects of such agents.

Although aerosol particles do not tend to settle on surfaces and may pass over the skin without depositing, except perhaps for hairy areas, the much larger particles that occur in a spray or a coarse dust are deposited more efficiently.

### 3.3.3 *Oronasal mucus and conjunctiva*

The mucosal tissues of the conjunctiva and the nasal passages are particularly sensitive to attack with irritant agents and the conjunctiva is especially sensitive to blister agents. Also, some infective agents, including variola, influenza and certain other viruses may enter through the oronasal mucus and, perhaps, the conjunctiva.

### 3.3.4 *Digestive system*

Biological and chemical agents can enter the digestive system via contaminated food or drinking-water, by hand-mouth contact after touching contaminated surfaces, or by swallowing of respiratory mucus after the accumulation of larger aerosol particles in the nose, throat and upper airways. Of all exposure routes, this is the easiest to control, provided that the contaminated sources are known (or at least suspected). Simple hygienic measures and control of supplies of food and drinking-water can significantly reduce the risk of exposure. If chemical agents are ingested, the delayed onset of symptoms (compared with respiratory exposure) and the increased prevalence of systemic rather than localized effects may lead to the conclusion that the persons

affected are suffering from a disease or general malaise or even that they have been exposed to a biological agent.

The problems presented by the direct biological contamination of food, water or other ingestible material are considered in Annex 5.

### 3.4 Characteristics of biological agents

The chief characteristic of biological agents defined on pages 5–6 above is their ability to multiply in a host. It is this that gives them their aggressive potential. The disease that may be caused results from the multifactorial interaction between the biological agent, the host (including the latter's immunological, nutritional and general health status) and the environment (e.g. sanitation, temperature, water quality, population density). The consequences of using biological agents to cause disease will reflect these complex interactions.

Biological agents are commonly classified according to their taxonomy, the most important taxa being fungi, bacteria and viruses. Such classification is important to medical services because of its implications for detection, identification, prophylaxis and treatment. Biological agents can also be classified according to properties that may determine their utility for hostile purposes, such as ease of production or resistance to prophylactic and therapeutic measures. More generally they can be characterized by such other features as infectivity, virulence, incubation period, lethality, contagiousness and mechanisms of transmission, and stability, all of which influence their potential for use as weapons

*Infectivity* of an agent reflects its capability to enter, survive and multiply in a host, and may be expressed as the proportion of persons in a given population exposed to a given dose who become infected. The dose that, under given conditions, infects half the population receiving it is termed the  $ID_{50}$ . Doses higher or lower than this will infect a larger or smaller proportion of such a population. For some pathogens the  $ID_{50}$  may be many thousands or more of infective cells or virus particles while for others it may be only a few. It cannot be ruled out that even a single infective cell or virus particle can initiate infection, albeit with correspondingly low probability.

*Virulence* is the relative severity of the disease caused by a microorganism. Different strains of the same species may cause diseases of different severity. Some strains of *Francisella tularensis*, for example, are much more virulent than others.

*The incubation period* is the time elapsing between exposure to an infective agent and the first appearance of the signs of disease associated with the infection. This is affected by many variables, including the agent, the route of entry, the dose and specific characteristics of the host.

*Lethality* reflects the ability of an agent to cause death in an infected population. The case-fatality rate is the proportion of patients clinically recognized as having a specified disease who die as a result of that illness within a specified time (e.g. during outbreaks of acute disease).

For those infections that are contagious, a measure of their *contagiousness* is the number of secondary cases arising under specified conditions from exposure to a primary case. The *mechanisms of transmission* involved may be direct or indirect. Thus transmission may, for example, result from direct contact between an infected and an uninfected person, or it may be mediated through inanimate material that has become contaminated with the agent, such as soil, blood, bedding, clothes, surgical instruments, water, food or milk. There may also be airborne or vector-borne secondary transmission. Airborne transmission can occur through coughing or sneezing, which may disseminate microbial droplets or aerosol. Vector-borne transmission (primary or secondary) can occur via biting insects, arthropods, or other invertebrate hosts. The distinction between types of transmission is important when methods for controlling contagion are being selected. Thus, direct transmission can be interrupted by appropriate individual hygienic practices and precautions and by proper handling of infected persons, caregivers and other contacts. The interruption of indirect transmission requires other approaches, such as adequate ventilation, boiling or chlorination of water, disinfection of surfaces, laundering of clothing or vector control.

*Stability* may refer to the ability of the aerosolized agent to survive the influence of environmental factors such as sunlight, air pollution,

surface forces and drying, while remaining infective. It may also refer to stability during production or to stability during storage.

### 3.5 Characteristics of chemical agents

As with biological agents, chemical agents may be classified in a variety of different ways depending on the type of characteristic that is of primary concern. This can lead to potentially confusing differences in the way that such agents are grouped and referred to in the literature. The most common characteristics are described below in order to introduce and explain frequently used terminology.

A common form of classification of chemical agents is according to the principal intended effect, e.g. harassing, incapacitating or lethal. A *harassing agent* disables exposed people for as long as they remain exposed. They are acutely aware of discomfort caused by the agent, but usually remain capable of removing themselves from exposure to it unless they are temporarily blinded or otherwise constrained. They will usually recover fully in a short time after exposure ends, and no medical treatment will be required. An *incapacitating agent* also disables, but people exposed to it may not be aware of their predicament, as with opioids and certain other psychotropic agents, or may be rendered unable to function or move away from the exposed environment. The effect may be prolonged, but recovery may be possible without specialized medical aid. A *lethal agent* causes the death of those exposed.

This is not a particularly precise way of classifying agents, as their effects will depend on the dose received and on the health and other factors determining the susceptibility to adverse effects of the individuals exposed. Tear gas (e.g. CS or CN), usually a harassing agent, can be lethal if a person is exposed to a large quantity in a small closed space. On the other hand, nerve agents, which are usually lethal, might only incapacitate if individuals were exposed to no more than a low concentration for a short time. Protective measures may be aimed at reducing the level of the effect if total protection is not possible. For example, the use of pretreatment and antidotes in a nerve gas victim

is unlikely to provide a complete “cure”, but may well reduce what would have been a lethal effect to an incapacitating one.

Another form of classification is according to the route of entry of the agent into the body (see pages 38–42 above). *Respiratory agents* are inhaled and either cause damage to the lungs, or are absorbed there and cause systemic effects. *Cutaneous agents* are absorbed through the skin, either damaging it (e.g. mustard gas) or gaining access to the body to cause systemic effects (e.g. nerve agents), or both. An agent may be taken up by either or both routes, depending on its physical properties or formulation.

A further classification is based on the duration of the hazard. *Persistent agents* will remain hazardous in the area where they are applied for long periods (sometimes up to a few weeks). They are generally substances of low volatility that contaminate surfaces and have the potential to damage the skin if they come into contact with it. A secondary danger is inhalation of any vapours that may be released. Persistent agents may consequently be used for creating obstacles, for contaminating strategic places or equipment, for area denial, or, finally, for causing casualties. Protective footwear and/or dermal protective clothing will often be required in contaminated areas, usually together with respiratory protection. Mustard gas and VX are persistent agents. *Non-persistent agents* are volatile substances that do not stay long in the area of application, but evaporate or disperse rapidly, and may consequently be used to cause casualties in an area that needs to be occupied soon afterwards. Surfaces are generally not contaminated, and the primary danger is from inhalation, and only secondarily from skin exposure. Respirators will be the main form of protection required. Protective clothing may not be necessary if concentrations are below skin toxicity levels. Hydrogen cyanide and phosgene are typical non-persistent agents.

Finally, chemical agents are often grouped according to their effect on the body, the classes being differentiated according to, for example, the primary organ system that is affected by exposure. Typical classes include: *nerve agents* or “gases” (e.g. sarin, VX, Vx); *vesicants* or skin-blistering agents (e.g. mustard gas, lewisite); *lung irritants*, *asphyxiants*

or choking agents (e.g. chlorine, phosgene); *blood* gases or systemic agents (e.g. hydrogen cyanide); sensory irritants (e.g. CN, CS, CR); and *psychotropic* or other centrally acting agents (e.g. the disabling agent BZ and the fentanyl opioids). This type of classification is used in Table 3.1 on page 33 above.

## 3.6 Consequences of using biological or chemical weapons

### 3.6.1 *Short-term consequences*

The most prominent short-term effect of biological or chemical weapons is the large number of casualties that they can cause, and it is this characteristic that determines most preparedness strategies. The potential for overwhelming medical resources and infrastructure is magnified by the fact that the psychological reaction, including possible terror and panic, of a civilian population to biological or chemical attack may be more serious than that caused by attack with conventional weapons. Psychological support strategies combined with risk communication are an integral part of the services needed to manage the many exposed and non-exposed casualties who may present at medical facilities (see Chapter 4). An instructive illustration of the nature of the short-term consequences of urban attack with chemical agents is provided by the 1994–1995 terrorist attacks in Japan in which the nerve gas sarin was used (see Appendix 4.2). The “anthrax letters” episode in the United States at the end of 2001, in which at the time of writing both the perpetrator and the motive remain to be discovered, provides some insight into the short-term consequences of biological agents being deliberately released (see Appendix 4.3).

Details of the short-term injuries caused by the various biological and chemical agents can be found in Annexes 1, 2 and 3.

### 3.6.2 *Long-term consequences*

The possible long-term consequences of the use of biological or chemical weapons, including delayed, prolonged and environmentally mediated health effects long after the time and place that the weapons were used, are more uncertain and less well understood.

Some biological and chemical agents have the potential to cause physical or mental illnesses that either remain, or only become evident, months or years after the weapons have been used. Such effects have long been recognized, and have been the subject of specific scientific monographs (5–6). They may extend the potential for harm of biological or chemical weapons beyond their immediate target both in time and space. For many agents too little is known about their long-term effects for reliable predictions to be made.

Such uncertainty carries over into the planning of medical counter-measures, and little more can be done than to outline the various possibilities needing further study. Non-military experience with disease-causing organisms, or with the presence of certain chemicals in the environment, may not be helpful guides to the effects of those same agents under the quite different conditions of deliberate release, in which greater quantities may be involved. However, useful pointers to what the consequences might be can sometimes be provided by the study of the effects of occupational exposure to chemicals. Organophosphate insecticides, e.g. methyl parathion, are hazardous for humans, and both the methods of treatment and the probable long-term effects of poisoning may be similar to those for nerve gases such as sarin.

The long-term health consequences of releases of biological or chemical agents may include chronic illness, delayed effects, new infectious diseases becoming endemic, and effects mediated by ecological changes.

The potential for *chronic illness* after exposure to some toxic chemicals and some infective agents is well known. The occurrence of chronic debilitating pulmonary disease in victims of exposure to mustard gas was reported after the First World War (7). This has also been described in reports on the current status of Iranian casualties from Iraqi mustard gas during the war between Iraq and the Islamic Republic of Iran in the 1980s (8–9). Follow-up of Iranian victims has revealed debilitating long-term disease of the lungs (chronic bronchitis, bronchiectasis, asthmatic bronchitis, pulmonary fibrosis, large airway obstructions), eyes (delayed mustard gas keratitis with blindness), and skin (dry and itchy skin, with multiple secondary complications,

pigmentation disorders, and structural abnormalities ranging from hypertrophy to atrophy). Deaths from pulmonary complications were still occurring as late as 12 years after all exposure had ended (10). Details of long-term effects caused by other toxicants are given in Annexes 1 and 2. Biological agents, including some of the agents of particular concern, may also cause long-lasting illness. *Brucella melitensis* infections, for example, which are typically more severe than brucellosis due to *B. suis* or *B. abortus*, especially affect bones, joints and heart (endocarditis). Relapses, fatigue, weight loss, general malaise and depression are common. *Francisella tularensis* infections result in prolonged malaise, and weakness may last for many months. The viral encephalitides may have permanent effects on the central and peripheral nervous system. Annex 3 provides further information.

The *delayed effects* in persons exposed to certain biological and chemical agents, depending on the dose received, may include carcinogenesis, teratogenesis and perhaps mutagenesis. Certain biological and chemical agents have been strongly implicated in the causation of cancer in humans, but it is not yet known whether infection by any of the microorganisms suited to biological weapons can be carcinogenic in humans, and only limited information is available on the ability of certain classes of chemicals to cause cancer, mainly in experimental animals. For example, some chemicals of particular concern, such as mustard gas, are alkylating agents, and many such agents have been found to be carcinogenic. While the evidence suggesting carcinogenesis after a single acute exposure to sulfur mustard is equivocal, there is good evidence of a significant increase in cancer of the respiratory tract among workers following prolonged low-dose exposure in factories producing mustard gas (11). Experiments with animals and epidemiological data for human populations show that the incidence of chemical carcinogenesis by many carcinogens depends on a power of the duration of exposure. Single exposures are therefore expected to be much less carcinogenic than months or years of exposure to the same total dose. Certain chemicals and infective agents can cause severe damage to the developing human fetus, thalidomide and the rubella virus being particularly well-known examples. It is not known whether any of the specific chemical or biological agents considered here will have teratogenic effects at the doses that could be

received by pregnant women in civilian populations that might be exposed to them. Little attention has been given to the possibility that known chemical and biological agents might cause detrimental heritable mutations in humans. Several chemicals are reported to cause such changes in experimental organisms and cultured human cells.

If biological agents are used to cause diseases that are not endemic in the country attacked, this may result in the *disease becoming endemic*, either in human populations, or in suitable vectors such as arthropods and other non-human hosts, such as rodents, birds, equids or cattle. *Bacillus anthracis* spores are highly resistant to environmental degradation, and can persist, particularly in soil, for long periods. By infecting and reproducing in animals, they can establish new foci. Microbes causing gastrointestinal infections in humans, such as *Salmonella* and *Shigella*, can establish persistent reservoirs. *Salmonella* strains can do likewise in domestic animals. A particular concern would be that a deliberate release of variola for hostile purposes could cause resurgence of smallpox, which was finally eradicated from natural occurrence in the 1970s, bringing special benefit to developing countries.

Finally, there is the possibility of *effects mediated by ecological change*. New foci of disease might become established as a result of ecological changes caused by the use of biological agents infective for humans and animals, or as a result of the use of anti-plant agents. These could have adverse long-term effects on human health via reductions in the quality and quantity of the food supply derived from plants or animals. They could also have major economic impact, either through direct effects on agriculture or through indirect effects on trade and tourism.

The broad conclusion to be drawn from the foregoing analysis is that there are great difficulties associated with assessing the long-term health effects of exposure to chemical and biological agents.

Confounding variables may affect the results of studies, and it may be difficult to distinguish genuine long-term effects of exposure from background occurrence of the same symptoms due to a wide spectrum of other causes. Conflicting data and inconclusive results often make it impossible to reach definitive conclusions.

Examples of the difficulties in determining the existence of long-term effects of chemical exposure have been provided by the ongoing investigations of medical problems apparently caused by the herbicide Agent Orange to people exposed in Viet Nam, where the chemical was widely used in the 1960s and early 1970s during the Viet Nam War (12). Investigations have paid special attention to the contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which is produced during manufacture and is persistent in the environment, detectable at elevated levels in sampled lipid and body fat, and highly toxic to certain experimental animals. In a more recent example, and with even less scientific evidence for a cause–effect relationship, chemical exposures of a variety of types were among the many factors suggested as potential causes of the so-called Gulf War syndrome. In both cases, a wide range of long-term symptoms and adverse health effects (including carcinogenesis, teratogenesis and a plethora of nonspecific somatic and psychological symptoms) are said to have been caused by exposure to chemical agents, among other possible causes (13). Despite intensive investigation, definitive explanations have not yet been found in either case.

### *3.6.3 Psychological warfare aspects*

Apart from their ability to cause physical injury and illness, biological and chemical agents may lend themselves to psychological warfare (which is a military term for attacks on morale including terrorization) because of the horror and dread that they can inspire. Even if the agents are not actually used, fear of them can cause disruption, even panic. Exacerbation of such effects can be expected from the exaggerated accounts of biological and chemical weapons that may arise in some circles. People may be better able to understand the harmful effects of conventional weapons than those of toxic or infective materials.

The emergence and spread of long-range missile delivery systems has increased the vulnerability to biological or chemical attack felt in cities, where the population may seem largely unprotectable, and this in turn has increased the psychological warfare potential. This was demonstrated in Teheran during the “war of the cities” in the final stage of the war between Iraq and the Islamic Republic of Iran in the 1980s when the threat – which never became a reality – that missiles might be

used to deliver chemical agents reportedly caused greater alarm than the high-explosive warheads actually used ever did. There was a further example of this during the Gulf War of 1990–1991, when it was feared that Scud missiles aimed at Israeli cities might be armed with chemical warheads. In addition to military and civil defence personnel, many civilians were issued with antichemical protective equipment and trained in procedures for chemical defence. Considerable disruption was caused since all missile strikes were regarded as chemical until proven otherwise, despite the fact that no chemical warheads were actually used by Iraq.

### 3.7 Assessment and conclusions

This chapter has introduced the wide variety of toxic and infective agents that could be used for hostile purposes. It has proposed that a relatively small group of agents, identified through the evaluation process that it describes, should form the focus of protective preparation. Preparedness can thereby be built against essentially all agents.

Of the various methods available for the release of biological and chemical agents, the major risk results from their dissemination as aerosols or, for some chemicals, as vapour. Respiratory protective equipment and means of predicting the potential spread of the airborne agent can allow timely protective measures to be taken in the areas that may be affected.

Skin exposure is a problem relating mostly to chemical agents and would usually occur only in the immediate vicinity of a release. Here, an important element of protection will be protective clothing. Skin protection may be required against both direct liquid exposure and high vapour concentrations. If a vapour risk exists, respiratory protection using adsorptive filters will also be required and in some cases evacuation of people from the hazardous area can be effective.

By understanding the general properties and potential consequences of the use of biological and chemical agents, a balanced approach to preparedness may be achieved. A preparedness programme should make provision not only for the immediate casualty-producing potential of such agents, but also for possible long-term consequences.

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