Chemical and Biological Weapons and Their Regulation

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Horst Thiermann, Kai Kehe, Julia Riehm, and Lothar Zöller

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Abstract

Chemical and biological agents have been used as weapons since ancient times. But it was only after the disastrous use of this type of agents in World War I that international efforts were made to prohibit them. These efforts were very

H. Thiermann (✉)
Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany
e-mail: HorstThiermann@bundeswehr.org

K. Kehe
Department F – CBRN Medical Defense, Military Medical Research and Development, Bundeswehr Medical Academy, Munich, Germany
e-mail: KaiKehe@bundeswehr.org; kai.kehe@lrz.uni-muenchen.de

J. Riehm · L. Zöller
Bundeswehr Institute of Microbiology, Munich, Germany
e-mail: JuliaRiehm@bundeswehr.org

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successful and continue until today. But nevertheless, it was not possible to forestall their use completely as shown recently by the events in Syria and most probably the attack on Kim Jong Nam. This chapter gives a short introduction in the field. It also characterizes some important agents and outlines, what is necessary to be prepared against a possible attack.

Introduction and History

Chemical warfare agents are chemicals, which have a very high toxicity and may therefore be misused as weapons to cause death or disease among the target population. For historical reasons, the term "chemical warfare" agent includes synthetic chemicals (toxicants) but usually does not include the toxins, which are poisons produced by living organisms. Toxin agents are often taken as a subgroup of biological agents (see below). However, for the toxicological risk assessment, there is no basic difference between toxicants and toxins. The disabling effect of such weapons on target persons is horrific. It is in the nature of such agents that they will without differentiation affect the exposed population.

It is probably a result of the widespread use of chemical weapons during World War I that international efforts were made, to restrict and ban such agents. In 1925, the use of asphyxiating, poisonous, or other gases and of bacteriological methods of warfare was prohibited and included in the Geneva Protocol. Mandatory regulations regarding the possession and development of warfare agents followed in 1968 (Chemical Weapons Convention) and 1972 (Biological Weapons Convention). On 29 April 1997 the Chemical Warfare convention entered into force, and 193 (data from today, one more nation is a member). Despite these regulations, several offenses occurred. The exile Bulgarian Markov died after an attack with ricin toxin in London in 1978. About 10 years later, members of the Japanese Aum Shinrikyo cult tried to poison attendants of a royal wedding party spraying medium supernatant from cultures of neurotoxin-producing *Clostridium botulinum* strains. According to the American "Working Group on Civilian Biodefense," 19,000 l of botulinum neurotoxin were produced during the 1990s in Iraq. Officially, there are no existent biological warfare programs nowadays. However, their presence cannot be completely denied as there are no legal control mechanisms. In 1995, the sarin subway attack was of terrorist origin. Such an attack is able to scare a whole nation and has high impact on politics and decision-making. In 2013, ricin toxin was used in a bioterror attack in the United States when three series of letters containing the substance were sent to officials and even the President. Although nobody was injured, the news attracted public attention and intensive media coverage worldwide. Chemical warfare agents are likely to be used in terrorist attacks as they are relatively easy to produce and designed to have a high lethality.

The use of poison in military conflicts is very old. One of the first attempts to use toxic substances in military operations was during the Cirraean war [595–585 BC].

The city of Kirrah was attacked by the Amphictyonic League of Delphi. A secret water supply of the city was poisoned with *Helleborus* roots. Helleborin caused severe diarrhea and weakened the defenders of the city. This is believed to be the first report of chemical warfare. Later in history, more toxic substances have been stockpiled and used as chemical weapons.

For example, historical documents claim the Assyrians to consciously poison their enemies by the application of *Claviceps purpurea*'s ergot in the sixth century BC. Later in time, one of Hannibal's warfare strategies aimed at throwing poisonous snakes on Pergamenes' ships.

Chemical warfare agents are still stockpiled and available for military use. After the last chemical war between Iran and Iraq 30 years ago, there was a long lag-period, in which there was no proof for the use of chemical or biological weapons in war. However, the situation changed dramatically, when in August 2013, news on a possible use of chemical weapons in a populated area in Syria made the headlines. Meanwhile, the use of sarin and sulfur mustard during the Syria crises was reported by the OPCW as having been verified and responsible for more than 1000 victims.

Chemical Weapons

Definitions

Article II of the Chemical Weapons Convention (CWC) defines a *toxic chemical* as "any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals." *Toxic chemicals* and/or devices (munitions) to disperse toxic chemicals are regarded as *chemical weapons*. Toxic chemicals, synthesized for military purposes, used in this context, are also called chemical weapon agents (CWAs). *Old chemical weapons* are produced before 1925.

CWAs are commonly classified as blood, blister, nerve, psychological, and pulmonary agents. This classification is commonly used but scientifically not correct, e.g., blood agents do not solely react with blood constituents. Blister agents may cause (more severe) systemic poisoning.

The CWC Annex of Chemicals distinguishes so-called Schedule 1–3 chemicals, which are regarded as CWAs.

Schedule 1 substances are toxic chemicals which have been used as chemical weapons or may be used for manufacturing chemical weapons (Table 1). Their civil use is limited. Some of the Schedule 1 chemicals have limited use in medicine or research. Saxitoxin and ricin are also Schedule 1 substances.

Toxic chemicals with possible use as chemical weapons or in their manufacturing process and which have legal use as well are listed in Schedule 2 (small-scale applications) and Schedule 3 (large-scale applications).

Table 1 Examples of chemical warfare agents listed in Schedule 1 and their physicochemical properties

Substance [NATO code]	Chemical name	CAS	MW	Boiling point [°C]	Freezing point [°C]	Vapor pressure [mmHg at 20 °C]	Vapor density [air = 1.0]	Solubility in water [g/100 g H_2O, 20 °C]
Schedule 1								
Sarin [GB]	Isopropyl methylphosphonofluoridate	107-44-8	140.1	158	−56	2.1	4.9	Miscible
Soman [GD]	Pinacolyl methylphosphonofluoridate	96-64-0	182.2	167–200	−42	0.4	6.3	2.1
Tabun [GA]	Dimethyl amidocyanoethylphosphate	77-81-6	162.1	220–246	−50	0.037	5.6	9.8
Cyclosarin [GF]	*O*-Cyclohexyl-methylfluorophosphonate	329-99-7	180.2	239	−30	0.044	6.2	0.37
VX	S-(2-diisopropyl aminoethyl) *O*-ethyl methyl phosphonothiolate	50782-69-9	267.4	298	−51	0.0007	9.2	3
HD	Bis(2-chloroethyl) sulfide	505-60-2	159.1	227.8	−50	0.072	5.6	<1

Characteristics of Chemical Weapon Agents (CWAs)

Nerve Agents

Organophosphorus (OP) compounds are widely used pesticides in agriculture. More than 160,000 deaths after OP poisoning occur worldwide. The main causes are of suicidal nature or accidents. A subgroup of OP compounds has highly toxic properties and was stockpiled as chemical weapons. OP nerve agents are divided into two groups: G agents and V agents. G agents contain a fluorine or cyanine as leaving group, whereas V agents contain a sulfur substituent leaving group.

Clinical Picture

OP poisoning shows typically the signs and symptoms of cholinergic crisis. Respiration is the most critical affected system. Severe poisoning causes respiratory depression, bronchosecretion, bronchospasm, and paralysis of respiratory muscles. Additional effects are miosis, increased secretions from glands, increased peristaltic activity, vomiting, general muscle weakness and twitching, hypothermia, bradycardia and hypotension, and convulsions followed by unconsciousness.

Toxicodynamic

Acetylcholinesterase (AChE) is one of the fastest-acting enzymes of the human body, which hydrolyzes the cholinergic transmitter acetylcholine (ACh), thereby inactivating its action on muscarinic or nicotinic receptors. Membrane-bound AChE is located at cholinergic synapses and neuromuscular junctions. Soluble AChE is present in the cerebrospinal fluid and in cholinergic nerve terminals. Nerve agents phosphorylate AChE at the active enzyme site, thereby inhibiting activity. As a consequence, ACh accumulates and overstimulates cholinergic receptors, leading to a cholinergic crisis. Antidotal therapy is directed either to competitively displace acetylcholine from the receptor (atropine) or to remove causally the nerve agent from its binding site (reactivation). To the later end, "reactivators" so-called oximes (e.g., obidoxime, pralidoxime) were introduced in causal therapy. This therapeutic strategy appears suitable in case of poisoning with several nerve agents (Sarin, VX). Unfortunately, however, AChE inhibited by several nerve agents can hardly be reactivated, e.g., tabun. Moreover, bound nerve agents undergo an "aging" process, where an alkyl or alkoxy group leaves the nerve agent AChE complex. The velocity of aging is dependent on the nerve agent and is extremely rapid in case of soman (aging half time about 2 min in humans). The "aged" complexes can no longer be reactivated. As a consequence, AChE reactivators as well as atropine should be given within minutes after exposure. Nevertheless, symptomatic treatment, e.g., artificial ventilation, may be necessary.

Biomonitoring, Bioanalytic, and Verification

To confirm clinical diagnosis based on typical signs and symptoms of cholinergic crisis, determination of red blood cell, AChE activity appears appropriate. This parameter can be determined even under field conditions or bedside within few minutes by the ChE-check mobile that is commercially available as certified as

medical products in Europe or in the United States by the Testmate®. Under several circumstances, however, ongoing treatment may be necessary, especially when active poison remains longer in the body than early administered antidotes. In such cases, aside from atropine, oxime treatment may be necessary for a longer period. To enable optimized patient-oriented application of oximes as long as needed, a laboratory test system, the so-called cholinesterase status, was established and is commercially available since early 2013. Apart from these clinically most relevant parameters, the analysis of intact nerve agent, its metabolites as well as protein and albumin adducts in body fluids are possible in special laboratories. However, for such analytical tasks, advanced techniques are necessary that are available only in a few laboratories.

Long-Term Effects

After exposure of organophosphate insecticides, an organophosphate-induced delayed neuropathy (OPIN) has been described. This clinical picture has not been observed in survivors of nerve agent poisoning. No reports about mutagenic, cancerogenic, or teratogenic effects after sarin, tabun, or VX poisoning have been published.

Vesicants

Sulfur mustard (bis(2-chloroethyl)sulfide, HD) was first synthesized in 1822 by Despretz. In World War I, it has been extensively used as chemical weapon and was called the "king of war gases." During World War II, nitrogen analogues such as ethylbis (2-chloroethyl)amine (HN-1), bis(2-chloroethyl)methylamine (mechlorethamine, HN-2), and tris(2-chloroethyl)amine (trichlormethine, HN-3) were synthesized in the United States. All these agents share their ability to induce skin blistering and were classified as "vesicants." Sulfur mustard is by far the most produced and stockpiled vesicant until today.

Clinical Picture (Short and Long Term)

Skin contact with sulfur mustard liquid or gas will produce blisters after a symptomless interval of several hours. Gaseous exposure affects more moist and hairy regions of the body as the genito-anal region, the chest, and axillae. The eyes are very susceptible. Even low vapor exposure results in ocular injury with severe blepharospasm. Inhalation of sulfur mustard vapor damages mainly the upper part of the respiratory tract. The trachea and bronchial epithelia become necrotic and detach from the wall (pseudomembranes). Besides this local effects, absorption of sulfur mustard results in systemic poisoning. Reproductive and developmental toxicity, gastrointestinal effects (vomiting, diarrhea), hematological effects (pancytopenia), and immunosuppression have been reported.

Toxicodynamic

Sulfur mustard is a lipophilic, alkylating substance with two reactive moieties. Sulfur mustard can easily penetrate the skin or other body surfaces and reacts with a huge variety of molecules. It can alkylate macromolecules and cross-link them.

The most important reaction is with the DNA. Sulfur mustard reacts predominantly with guanine at the N_7 position, which accounted for 61% of total DNA alkylation. Less likely are cross-links, 17% of alkylations involve two guanines (G-alkyl-G). However, cross-linked DNA strands are difficult to repair and cell division may result in DNA strand breaks, which are lethal lesions of the cell. Apoptotic cell death occurs with a delay of several hours.

This explains the late onset of clinical symptoms in organs characterized by high cell proliferation (e.g., skin). Despite a century of research and deeper insight in the pathophysiology of sulfur mustard poisoning, no causal treatment has been identified so far.

Late Effects

Sulfur mustard poisoning results in a variety of late effects. The most common late effects were found in the respiratory tract (42.5%), eyes (39%), and skin (24.5%).

The most disabling late effects after sulfur mustard inhalation are respiratory disorders, e.g., bronchiolitis obliterans, chronic obstructive pulmonary disease, asthmatoid bronchitis, and bronchial stenosis.

Late effects at the eyes are chronic keratoconjunctivitis. Only a few of exposed soldiers (0.5%) complain of a delayed type of ulcerative keratitis, which occurs several years after exposure and results in opacification of the cornea.

Balali-Mood et al. (2005) published a study on soldiers heavily exposed to sulfur mustard. The most important dermatological late effects are hyperpigmentation (55%), hypopigmentation (25%), erythematous papular rash (42.5%), dry skin (40%), multiple cherry angiomas (37.5%), and skin atrophy (27.5%).

As a DNA-damaging agent, it has been linked to several forms of cancer observed in workers or soldiers. Lung cancer (e.g., adenocarcinoma) has been reported in workers of sulfur mustard production facilities. Skin cancer (e.g., basalioma) may occur at exposed sites.

Biological Weapons

Definition

Biological weapons may be used for strategic or tactical reasons to intimidate, incapacitate, or kill an opponent, single individuals, or entire groups. The highest risk of a deliberate release of a biothreat agent currently arises from bioterrorism. Numerous species of highly infectious bacteria or viruses and various biological toxins have been misused as biological warfare agents in the past or are associated with an inherent risk to be misused due to their specific properties. Moreover, some species of fungi and parasites are listed as potential biothreat agents by some authors. Listing and current ranking of biothreat agents can be accessed at the websites of the American CDC, in the Chemical Weapons Convention, in the textbook of military medicine, or in the NATO handbook on the medical aspects of NBC defensive operations (AMedP-6(B)).

Among the biological warfare agents, biological toxins in contrast to live bacteria and viruses represent a group of noninfectious substances. Only toxins that can be utilized independently of their producer organisms are considered as autonomous biothreat agents and must be differentiated from toxins that are produced by the microorganisms during the course of infection and act as pathogenicity factors, such as the toxins of *Bacillus anthracis*. Biothreat toxins may cause Incapacitation, severe intoxication, or even death in exposed humans or animals. Early in history, various poisonous substances used to be employed not only for man's own survival but also to attack enemies. For the toxicologist, the risk assessment of toxin-derived "biological warfare agents" is principally the same as that of chemical warfare agents.

Characteristics of Biological Toxins

Toxins represent a subset of biothreat agents, which are also called mid-spectrum agents. They are noninfectious and do not reproduce in the host. The clinical manifestations of toxin-related diseases usually appear after a shorter latency period as compared to infectious agents. Naturally occurring biological toxins are synthesized by plants (curare, ricin), fungi (aflatoxins), amphibians (dart frog's batrachotoxin), bacteria (botulinum neurotoxin), or algae (paralytic shellfish poison) and are mostly part of the self-protection strategies of the producing organisms. The structures of biological toxins range from complexly assembled structures to simple bioregulator molecules: Complex AB toxins are produced by bacteria or plants. They consist of a binding (B) and an active (A) domain and interfere with internal cell functions. The binding subunit (B) binds to a cell surface receptor and enables the transport of the cytotoxic A-subunit into the cell. The sizes of AB toxins range from 25 kD to 200 kD (Table 2). Other toxins are non-peptide substances and rather bioregulator molecules. Their onset of action is immediate in contrast to AB toxins, which take effect with a latency period of hours, sometimes days. Their molar mass is smaller, ranging from 300 g/mol to 3000 g/mol (Table 2). They are also markedly stable under various environmental conditions, versus heat and pH alterations. They can even be synthesized in vitro (STX), which is not possible for the proteinaceous toxins. The trichothecene mycotoxins belong to the non-peptide substances and, moreover, are contact poisons. They gained notoriety as the "yellow rain" agent during the 1970s and 1980s in Cambodia and Laos, Southeast Asia, which is – for lack of unambiguous evidence – not without controversy.

Toxicological effects of biological toxins were studied mostly after alimentary uptake. However, more severe physiological consequences may result from exposure through a non-enteric route. Intentional exposure to toxins in aerosol and droplet clouds and after subcutaneous injection has occurred. Yet only few and inconsistent data is available with regard to the associated health effects. A variety of nonspecific clinical symptoms and multiorgan effects may develop depending on the way of exposure, ranging from acute emesis and diarrhea, nervous disorders,

Table 2 Characteristics of a selection of biological toxins without subtype differentiation

Origin	Name	Short	Listing	Main effect	Main pathophysiology	LD_{50}	Specific prophylaxis/ treatment	Size (kD)	Gold standard detection
Bacteria									
Clostridium botulinum	Botulinum neurotoxins	BoNT	AMedP-6(B) Cat A (CDC)	AB toxin, neurotoxic	Flaccid paralysis, botulism	0.001i.v; 1 p.o.	Antiserum, vaccine (limited)	160	Mouse bioassay
Clostridium perfringens	Epsilon toxin	–	AMedP-6(B) Cat B (CDC)	Pore-forming toxin, potassium, and fluid leakage from cells	Vasogenic brain edemas, indirect neuronal excitotoxicity	0.5	–	30	Mouse neutralization test
Staphylococcus aureus	Enterotoxins	SE	AMedP-6(B)	Emetic, toxic shock syndrome	Emesis, T-cell stimulation, cytokine release	0,02 inh	–	25	ELISA
Algae/plankton									
	Saxitoxin/ paralytic shellfish toxin	STX/ PST	AMedP-6(B) CWC	Neurotoxic, sodium channel blockage	Flaccid paralysis	6	–	0.3	Mass spectrometry
Plant									
Ricinus communis	Ricin	–	AMedP-6(B) CWC Cat B (CDC)	AB toxin, inhibition of protein synthesis, cytotoxic	Tachycardia, hypotension, seizures, multiorgan dysfunction	3i.v., >1000 p.o.	Vaccine in development	65	In vitro bioassay

(continued)

Table 2 (continued)

Origin	Name	Short	Listing	Main effect	Main pathophysiology	LD_{50}	Specific prophylaxis/ treatment	Size (kD)	Gold standard detection
Abrus sp.	Abrin	–		AB toxin, inhibition of protein synthesis, cytotoxic	Multiorgan dysfunction	>0.03i. v.;>10 p.o.	–	65	n.d.
Fungus									
Fusarium sp.	Trichothecene		AMedP-6(B)	Inhibition of protein synthesis					LC-MS/MS
	Deoxynivalenol	DON		Inhibition of protein synthesis	Emesis	10E7		0.3	LC-MS/MS
	T-2 mycotoxin	T-2		Inhibition of protein synthesis	Aleukia, cancerogenic	10E3	–	0.47	LC-MS/MS

Abbreviations: LD_{50} human LD_{50} (μg/kg), *i.v.* intravenously, *p.o.* per os, *inh.* inhaled

cardiovascular alterations, hemostatic derangements, skin toxicity, and multiorgan failure to chronic syndromes such as immunosuppression, weight loss, decreased reproductive capacity, and bone marrow damage.

Risk Assessment Aspects

Due to their relative ease of production and immense toxicity, some biological toxins are considered as potential biological warfare agents. The Centers for Disease Control (CDC, Atlanta, United States) provide the most widely used priority categorization of bioterrorism agents according to the risk to national security associated with them. Features determining the categorization are the ease of transmission/dissemination, the mortality rates, and the public health impact. The botulinum neurotoxins are classified as category A (highest priority). Ricin, staphylococcal enterotoxins, further clostridial toxins, and cholera toxin are classified as category B (second priority) agents. As listed in Table 2, biological toxins are also considered in the NATO handbook on the medical aspects of NBC defensive operations (AMedP-6 (B)) and most officially in the Chemical Weapons Convention.

In a military scenario, ricin and the botulinum neurotoxins are – besides the causative agents of anthrax or pneumonic plague – also considered as high-risk agents for bioterroristic or warfare activities. Risk-ranking respects the dimension of damage and the probability of an intentional event associated with the respective substance in a given scenario.

Low-dose pharmaceutical drugs containing botulinum neurotoxin (Botox) are commercially produced for the medical treatment of various neurological syndromes (Dysport®, Ipsen Biopharmaceuticals; Myobloc® Solstice Neurosciences; Botox®, Allergan). Moreover, in recent years, the cosmetics industry has established a fairly new market for botulinum neurotoxin due to its effect of wrinkle reduction. Every year, around 75 billion dollars are reaped with such products, which has given rise to large-scale non-licensed production of Botox drugs that are distributed via the internet. Illegal Botox production plants have settled in China, India, and the successor states of the former Soviet Union and might become a potential toxin source for bioterrorists. Ricin was researched for its ability to kill tumor cells during cancer treatment. However, pharmaceutical products have never emerged from such scientific approaches.

Risk Management

Biological Weapons Convention (BWC)

The BWC is an international agreement on the prohibition of the development, production, and stockpiling of bacteriological (biological) and toxin weapons and on their destruction. It was implemented in 1975 as a first multilateral disarmament agreement based upon the 1925 Geneva Protocol. It lacks the listing and ranking of

possible agents. So far, the BWC has 179 member states and 6 signatories. Eleven states have neither signed nor ratified the BWC. A major shortcoming of the BWC is its lack of a verification regime, which makes it difficult to prosecute noncompliance.

Chemical Weapons Convention (CWC)

Organization for the Prohibition of Chemical Weapons (OPCW)

Since 1997, the OPCW, located in The Hague, Netherlands, has been authorized to execute the controls and sanctions regarding the CWC as the official implementing body. Today, the organization comprises 193 member states and is directly responsible to the United Nations committee. OPCW received the Nobel Peace Prize in the year 2013.

To fulfill its tasks, the OPCW is comprised of several organs: the Technical Secretariat regulates administration, controls verification of international CWC implementation, and coordinates routine inspections. In return, decisions are made by the Executive Council and the Conference of the States Parties. They resolve questions of policy and matters arising between the States Parties on technical issues or on interpretations of the Convention.

Two of the biological toxins are listed in Annex B, Schedule 1, Numbers 7 (saxitoxin) and 8 (ricin).

National Regulations: Installation of Preparedness Standards

Laboratory Safety

As regulated in the CWC, the production, acquisition, and handling of quantities of more than 100 grams of a listed agent per year require permission. For the time being, only a few biological toxins are available in small amounts in the free market for research, analytical, or therapeutic issues.

Regarding safety at work on biological toxins in Germany, a national Committee on Biological Agents establishes or adapts the rules, which are officially released by the Federal Ministry of Labour and Social Affairs as Technical Rules for Biological Agents (TRBA). The most basic documents are the following TRBAs: “Protective Measures for Specific and Non-specific Activities involving Biological Agents in Laboratories” (TRBA 100) and “Basic Measures to be taken for Activities involving Biological Agents” (TRBA 500). Accordingly, handling of biological toxins is allowed in laboratories at containment level 1 (toxins) or a higher containment level corresponding to the risk group of an associated organism (e.g., level 2 for *Clostridium botulinum* strains). According to the international Globally Harmonized System of Classification and Labeling of Chemicals (GHS), tagging of vials containing biological toxins is required by use of a pictogram and a signal word (i.e., “Danger” or “Hazard”). Additionally, an individual material safety data sheet is required for each substance or mixture that mandatorily lists all hazard and precautionary statements.

Table 3 AEGL values (mg/m^3) for selected chemical warfare agents (Watson et al. 2006)

		Sarin (GB)	Tabun (GA)	Soman (GD)	Cyclosarin (GF)	VX
AEGL-1	10 min	0.00690	0.00690	0.00350	0.00350	0.00057
	30 min	0.00400	0.00400	0.00200	0.00200	0.00033
	1 h	0.00280	0.00280	0.00140	0.00140	0.00017
	4 h	0.00140	0.00140	0.00070	0.00070	0.00010
	8 h	0.00100	0.00100	0.00050	0.00050	0.00007
AEGL-2	10 min	0.08700	0.08700	0.04400	0.04400	0.00720
	30 min	0.05000	0.05000	0.02500	0.02500	0.00420
	1 h	0.03500	0.03500	0.01800	0.01800	0.00290
	4 h	0.01700	0.01700	0.00850	0.00850	0.00150
	8 h	0.01300	0.01300	0.00650	0.00650	0.00100
AEGL-3	10 min	0.38000	0.76000	0.38000	0.38000	0.02900
	30 min	0.19000	0.38000	0.19000	0.19000	0.01500
	1 h	0.13000	0.26000	0.13000	0.13000	0.01000
	4 h	0.07000	0.14000	0.07000	0.07000	0.00520
	8 h	0.05100	0.10000	0.05100	0.05100	0.00380

Risk Management

Besides international regulations to reduce the stockpiles of chemical warfare agents, national regulations are necessary to reduce health risks for the general population and emergency personnel. As the risk for terrorist attacks with chemical warfare agents or similar substances rises, toxicity estimates and exposure guidelines have been recently updated to ensure a more realistic national preparedness. In the United States, Acute Exposure Guideline Levels (AEGLs) have been developed and published (Watson et al. 2006). AEGLs were calculated for vapor exposure (10 min–8 h). AEGL-1 has been defined as a threshold where first mild symptoms are noticed, e.g., miosis for nerve agents. On the other hand, AEGL-3 vapor concentrations may induce severe life-threatening health effects. The published data (Table 3) can be used for planning and risk management to counteract terrorist attacks with chemical warfare agents.

Laboratory Standardization Approaches

Since 2012, an expert laboratory network has been constituted for the Establishment of Quality Assurance for the Detection of Biological Toxins of Potential Bioterrorism Risk (EQuATox), which since 2016 is continued in the Horizon 2020 funded network European program for the establishment of validated procedures for the detection and identification of biological toxins (EuroBioTox). Its goal is to build up a network of European laboratories that use equal standards for the detection and identification of biotoxins. The network is about to develop and validate improved analytical tools, reagents, reference materials, and standard operating procedures based on realistic incident scenarios. After comprehensive proficiency testings, best practice procedures will be determined and disseminated across Europe.

Pharmacy

The availability and development of antidotes against chemical warfare agents is a continuous challenge. For several chemical warfare agents, e.g., mustard, no specific antidote exists in spite of decades of research. In recent years, new technologies were developed, allowing a deeper insight into the mechanism of toxicity, and new approaches are under investigation possibly enabling improved wound healing. In other cases, e.g., nerve agents, new autoinjectors containing an oxime, atropine, and benzodiazepam are under development. As commercial interest in antidote development generally is very low, national financial support is crucial to sustain research efforts and to allow development of new devices, e.g., autoinjectors or new promising approaches to improve therapy.

During World War II, toxoid vaccines were investigated by the United States to protect researchers working on the production of biological warfare agents. Since then, further vaccines against biological toxins have been developed, among them the pentavalent PBT vaccine (CDC) against five serotypes of botulinum neurotoxin, the RiVax™ Ricin Toxin Vaccine (Soligenix), and a candidate vaccine against staphylococcal enterotoxin B (USAMRIID).

A very limited number of heterologous antitoxin products are available for the treatment of botulism (e.g., trivalent Botulismus-Antitoxin Behring, Novartis, heptavalent BAT® Emergent BioSolutions Inc. (FDA approved)). Besides the few specific treatment options, therapy relies on supportive measures and in most cases requires intensive care facilities.

A network of specific poison control centers is available throughout European countries. They are associated with local hospitals and store antitoxins and provide expertise regarding the treatment of intoxications.

Decontamination

Decontamination of body parts after exposure to chemical warfare agents or biological toxins is accomplished by cleaning with soap and water. Pharmaceutical products such as Reactive Skin Decontamination Lotion (RSDL) may be used for decontamination of skin surfaces contaminated with chemical warfare agents or biological toxins with skin absorption (trichothecene group) (Table 2). Wounds and lesions may be flushed with physiological solutions. For the decontamination of equipment, protein-denaturing dilutions of sodium or calcium hypochlorite may be used.

Cross-References

- ► Checklist: Toxicological Risk Assessment in Practice
- ► Data Mining in Toxicology
- ► Importance of Physicochemical and Physical Properties for Toxicological Risk Assessment
- ► Principles of Analytical Chemistry for Toxicology

▶ Risk Communication: Challenges for Toxicologists and Other Risk Experts
▶ Risk Management in Toxicological Disasters
▶ Toxicity Testing In Vitro: Regulatory Aspects
▶ Toxicological Risk Assessment

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