

# **Practical Guide for Medical Management of Chemical Warfare Casualties**



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Medical Management of  
Chemical Warfare Casualties**



**OPCW**

**Organisation for the Prohibition of Chemical Weapons**

**International Cooperation and Assistance Division**

**Assistance and Protection Branch**

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## Foreword

One hundred years ago, near Ieper in the fields of Flanders, humankind witnessed the advent of a new kind of warfare. On the 22<sup>nd</sup> of April 1915, chemical weapons were used for the first time on a large scale. This chemical weapon attack was the first of what was to become a common method of warfare for the remainder of the First World War.

By the end of World War I, more than 1.3 million people had become victims of chemical warfare (CW), and more than 100,000 of these CW casualties died shortly after their exposure to CW agents. Many thousands of the other CW casualties who survived the conflict suffered the long-term effects of chemical agents, including serious respiratory health issues, for the rest of their lives.

Tragically, World War I was only the opening chapter in a century-long history of chemical warfare. In the decades following World War I, humankind has lived under the threat of massive chemical arsenals one day being used again on a large scale. Despite the efforts of the international community to prohibit chemical warfare, chemical weapons were used in many conflicts throughout of the 20<sup>th</sup> century, notably by Saddam's regime during the Iraq-Iran War, causing many thousands of casualties among civilians and combatants alike in towns such as Sardasht and Halabja. Such weapons have also been used during the armed conflict in Syria.

At the end of diplomatic efforts spanning almost a century to eliminate the use of chemical warfare agents, the text of the Chemical Weapons Convention (CWC) was finally adopted in 1992, with the objectives of ridding the world of the existing chemical weapons stockpiles, and preventing the re-emergence of such weapons.

Under the auspices of the CWC, the Organisation for the Prohibition of Chemical Weapons (OPCW) has built up a verification and monitoring regime that inspires confidence and renders tangible results. The Organisation has also developed a network of assistance and protection that enhances global security and it has fostered international cooperation that encourages the peaceful uses of chemistry for the benefit of all. It is within this spirit of international cooperation and in recognition of the importance of providing assistance to victims of chemical weapons, that the OPCW has commissioned this manual for medical practitioners who care for the victims of chemical warfare.

Development of this Guide was the result of the efforts of a team of internationally recognised experts in the field of medical treatment of chemical weapons injuries, brought together at the invitation of the OPCW. Under the leadership of Professor Balali-Mood, the authors volunteered countless hours to the preparation, drafting and review of this excellent resource document. The collaborative efforts of this team of scholars were also made possible by the generosity of Dr. Robert Mathews, who won the inaugural OPCW-The Hague Peace Award and donated his cash prize to the Trust Fund for the International Support Network for the Victims of Chemical Weapons, which funded the project. On behalf of all who will benefit from this publication, I would like to express my gratitude to each of the distinguished contributors to this important work.

Finally, as I reflect upon the contributions of the CWC and the OPCW to international disarmament efforts over the ninety-seven years since a general armistice put an end to the Great War, it is my profound aspiration that this Guide will never need to be called upon to serve its intended purpose. Failing that however, I very much hope that it will provide valuable guidance to medical practitioners in the treatment of casualties of chemical weapons and thereby help to alleviate the suffering of any future victims of these unlawful and inhumane weapons.

Ahmet Üzümcü

OPCW Director-General

The Hague, 11 November 2015



## Preface

In recognition of the importance of providing assistance to victims of chemical weapons, the Organisation for the Prohibition of Chemical Weapons (OPCW) has developed this Guide for medical practitioners who care for the victims of chemical warfare.

Chapter 1 of this Guide provides medical practitioners with an appreciation of the history of the development and use of chemical weapons, the types of chemicals which have been used as chemical weapons and a brief summary of the efforts of the international community to prohibit the use of such chemicals.

Chapter 2 of the Guide deals with the general considerations in management of chemical casualties, and provides an overview of basic concepts that should be considered by medical personnel involved in the management of a chemical weapon incident.

Chapters 3 to 8 of the Guide deal with the medical management of casualties caused by: Vesicants (blister agents); nerve agents; lung-damaging (choking) agents; blood agents; riot control agents (sensory irritants); and toxins (in particular ricin plant toxin and saxitoxin marine toxin), respectively. Issues covered for each class of chemical

warfare agents include their mechanism of toxicity, signs and symptoms occurring after an acute exposure, clinical management and treatment. Where applicable, attention is also drawn to the possible occurrence of long term effects caused by exposure to the various classes of chemical warfare agents.

Chapter 9 of the Guide provides a summary of the earlier chapters and concluding comments.

The Guide also includes a number of annexes providing relevant background information on: the Chemical Weapons Convention; the classes of chemical warfare agents which have considered in this guidebook; preliminary information on some of the other toxic chemicals that could also be used as chemical warfare agents; a diagram to assist with the preliminary identification of which classes of chemical warfare agents a casualty may have been exposed to, based on the initial symptoms; and information on the long term consequences of exposure to various chemical warfare agents.

The Guide also includes a list of abbreviation and glossary of the terms used in this document.

The authors would like to acknowledge Dr Shahriar Khateri of the Assistance and Protection Branch in the OPCW Technical Secretariat, whose dedication and tireless support to our efforts was an essential element in the successful conclusion of this endeavour.

In closing, we very much hope that this Guide will provide valuable guidance to medical practitioners in the clinical management and treatment of casualties of chemical weapons.

Mahdi Balali-Mood

Paul Rice

Jan Willems

Robert Mathews

James Romano

Rene Pita

Horst Thiermann

## **Chapter 1:**

### **Introduction and historical overview**

The use of poisons and poisoned weapons as a method of warfare has been practised since ancient times, ranging from poisoned arrows and spears, to poisoning wells and food supplies, to the dispersion of toxic vapours and smokes. For example, the use of toxic chemicals as a method of warfare dates at least as far back as the 7th century, when the Byzantine navy used 'Greek fire', typically a mixture of sulphur and naphtha which, when burnt, caused both toxic and incendiary effects. A range of other toxic chemicals were used, including arsenic-containing chemicals.

The prohibition of the use in warfare of poisons seems almost as ancient as the weapons themselves. The earliest surviving pertinent references include the Manu laws of India (dating from prior to 500 BC), which prohibited the use of poisoned weapons, as well as ancient Chinese, Greek, and Roman law, and law derived from the Koran. Thus, in these historical times, it was generally accepted that the use of poisons and poisoned weapons in armed conflict was contrary to the law of nations.

However, until the rapid development of the chemical industry in the late 19th century, which enabled the production of large quantities of toxic chemicals, the use of chemical weapons was not considered particularly suitable as a method of warfare. The concerns that these developments in the chemical industry could bring about a practical method of warfare led to the negotiation of the prohibition of ‘poisons and poisoned weapons’ as a method of warfare in the 1899 and 1907 Hague Conventions, as well as the negotiation of a declaration to ‘abstain’ from using projectiles that could spread ‘asphyxiating or deleterious gases’.

However, the limited effectiveness of the prohibitions included in the provisions of the Hague Conventions soon became apparent with the extensive use of chemical weapons during World War I. Initially, small quantities of a number of sensory irritants (including xylol bromide and ethyl bromoacetate tear gases) were used in 1914 by the French troops against the Germans, but were not considered particularly effective. However, everything changed on 22 April 1915, when German troops made a massive gas attack at Ieper in Belgium. A total of more than 150 tonnes of the choking agent chlorine was released and allowed to drift over Allied forces from approximately 6,000 gas cylinders along a front extending over several kilometres. This caused several thousands of casualties, including up to 5,000 deaths, and resulted in a temporary break in the Allied lines. But the impact of the attack took both sides by surprise and the Allied forces had re-established their positions before the German troops could take military advantage of the situation.

In late 1915, the German military began using another choking agent (phosgene), and the use of gas cylinders as a method of delivery was soon replaced by artillery shells including mortars. In early 1916, the Allies (who from April 1915 had rapidly increased their industrial capability for the production of sufficient quantities of chlorine and other toxic chemicals for warfare purposes) began using large quantities of choking agents against German troops.



**Figure 1.1:** *Soldiers wearing anti-phosgene masks during World War I*

In early 1916, the French troops began using the blood agent hydrogen cyanide. However, because hydrogen cyanide is lighter than air, it was difficult to generate significant concentrations on the battlefield, and there was limited military advantage in the use of this chemical warfare (CW) agent. The French subsequently weaponised another blood agent, cyanogen chloride, but it was not considered as effective as phosgene.

The large numbers of casualties occurring in the early chemical weapons attacks were primarily because the troops lacked effective respiratory protection. Within months of the first large-scale chemical weapons attack in April 1915, both sides had developed rudimentary gas masks (respirators), which were able to greatly reduce the battlefield effectiveness of the volatile choking and blood agents (Figure 1). This led Germany to produce and weaponise the blister agent sulphur mustard, at that time commonly called ‘mustard gas’. When first used near Ieper on 12 July 1917, sulphur mustard caused large numbers of casualties by affecting the skin, eyes, and respiratory tract (Figure 1.2). The British, French, and Americans began using sulphur mustard shortly after. This led to the development of early forms of CW protective suits (including the use of oiled cloth, which provided resistance to liquid CW agents).



**Figure 1.2:** *Soldiers temporarily blinded following exposure to sulphur mustard in 1917*

There was typically a latent period of up to several hours between exposure to sulphur mustard and the development of symptoms. Then, in 1917, an American chemist, Dr W. Lee Lewis developed a new vesicant (blister agent), subsequently named Lewisite, that produced immediate pain on contact with the skin. The United States (US) was ready to ship Lewisite-containing munitions in November 1918 when the armistice was agreed. However, Lewisite was subsequently weaponised (prior to World War II), including by Japan, Russia, Britain, and the US, and often mixed with sulphur mustard as a means to reduce the freezing point of sulphur mustard.

More than 1.3 million people (primarily combatants) were injured by chemical weapons in World War I, and more than 100,000 of these chemical weapons casualties died shortly after their exposure to CW agents. Many thousands of those who survived the conflict suffered the long-term effects of chemical agents for the rest of their lives. Altogether, more than 125,000 tonnes of toxic chemicals were used on the battlefield.

The large scale of use of chemical weapons during World War I was widely condemned by the international community. For example, in an appeal to the belligerents on 6 February 1918, the International Committee of the Red Cross stated that:

We wish to-day to take a stand against a barbaric innovation ... This innovation is the use of asphyxiating and poisonous gas, which will it seems increase to an extent so far undreamed of ... We protest with all the force at our command against such warfare which can only be called criminal.

This led to the negotiation of the 1925 Geneva Protocol by the League of Nations. The Protocol prohibited the use of chemical and biological weapons, but not the development, production and stockpiling of chemical and biological weapons. The Protocol was promptly ratified by most major military powers with the exception of Japan and the US (which eventually ratified in 1975). Many States which ratified the Protocol did so with the reservation that they would be permitted to use chemical weapons in retaliation if another State used chemical weapons against it first.

Unfortunately the 1925 Geneva Protocol did not prevent the use of chemical weapons, even in international conflicts between States Parties of the Protocol (Table 1.1).

In 1936 and 1937, Italy used a number of CW agents including diphenylchloroarsine (sometimes referred to as a tear gas, but having long-term toxic effects) and sulphur mustard in the war against Abyssinia. The results were so devastating and had a decisive influence on the outcome of the war because the Abyssinians did not have any form of protection against chemical weapons.

In the 1930s, chemical companies in Germany were undertaking research into improved insecticides and discovered very toxic organophosphorus compounds. The military authorities were informed and this led to the development of the nerve agents tabun and then sarin. Tabun was produced for the first time in December 1936 and was being

manufactured and weaponised by 1939. During World War II, Germany produced several thousand tonnes of tabun and smaller amounts of sarin. Despite being the only country to possess stockpiles of nerve agents in World War II, Germany never attempted to use them, at least in part because the German military were under the impression that the British had also developed their own nerve agent production. Thus, chemical weapons were not used in the European theatre in World War II. However, on the night of 2 December 1943, German aircraft attacked the port of Bari in southern Italy, sinking several American ships—among them the SS John Harvey, which was carrying sulphur mustard intended for use in retaliation by the Allies if German forces initiated chemical warfare. The leakage of the sulphur mustard resulted in 628 mustard military casualties, including 69 deaths, among them American merchant seamen, and a large but unknown number of civilian casualties.

In another arena, Japan had commenced producing and weaponising large quantities CW agents by the mid-1930s, and in its conflict with China between 1937 and 1945 it used a number of CW agents, including hydrogen cyanide, phosgene, sulphur mustard, and sulphur mustard/Lewisite mixtures (H/L). It has been reported that there were many thousands of Chinese chemical weapons casualties resulting from more than 2,000 separate chemical weapon attacks by Japan. At the end of the war, a large part of the unused Japanese chemical weapons stockpile was left in China (Figure 1.3), and this has resulted in many casualties in subsequent decades (these stockpiles of ‘abandoned’ chemical weapons are currently being destroyed under the provisions of the Chemical Weapons Convention).





**Figure 1.3:** *Excavation and recovery of abandoned Japanese chemical weapons in China*

At the end of World War II, the German chemical weapons stockpiles were taken over by the Allies, and much of the Allied and German chemical weapons stockpiles were destroyed, either by venting into the atmosphere (phosgene), open-pit burning, or sea dumping. It is estimated that more than 200,000 tonnes of CW agents, primarily blister agents, were dumped at sea. The CW agents dumped at sea have subsequently caused major health, safety, and environmental concerns in some locations, most notably when buried in the relatively shallow waters used by fishermen in the Baltic Sea.

In the early 1950s, industrial research in the United Kingdom attempting to develop more effective pesticides led to the discovery of the nerve agent amiton, which was used for a short time in agriculture, but was then withdrawn because of its high mammalian

toxicity. It was subsequently discovered that replacing one of the phosphorus-alkoxy bonds in amiton with a phosphorus-methyl bond increased the toxicity by at least a factor of 10. This led to the development and weaponisation of the V-series of nerve agents, with the development and weaponisation of VX by the US, and the development and weaponisation of homologues of VX by other countries (for example, Vx by the former Soviet Union). Not surprisingly, the physical and toxicological properties of VX and homologues of VX are similar, and methods of medical treatment of exposure to the V-series agents are also very similar.

In 1968, more than 6,000 sheep grazing near the US Army Dugway Proving Ground in Utah died during a VX field exercise that had 'gone wrong'. The resulting public protest led to the cessation of all US open-air testing of CW agents, and the termination of chemical weapons production by the US for almost 20 years. Another issue which caused public protest (both in the US and internationally) was the widespread use of tear gas and herbicides by the US Army in the Vietnam War. At the time, the US military argued that the use of these chemicals was not prohibited by the 1925 Geneva Protocol. However, in 1975 US President Gerald Ford issued an Executive Order (11850) strictly limiting the use of tear gas and herbicides in military conflict to 'defensive purposes', and the US also ratified the 1925 Geneva Protocol in the same year.

During the 1960s, the US and the former Soviet Union were both actively developing psychochemical warfare agents, including BZ which was weaponised by the US. However, there was uncertainty about the effectiveness of this class of CW agents and both countries chose to destroy their stockpiles in the 1980s.

Between 1976 and 1980, the US and the former Soviet Union convened a series of bilateral meetings with the objective of developing an agreement for the complete elimination of all chemical weapons stockpiles. The positive outcomes from these discussions paved the way for the negotiation of the Chemical Weapons Convention in the Conference on Disarmament at the United Nations in Geneva.

Concerns in the early 1980s about the production and alleged use of chemical weapons led to the adoption of the UN Secretary-General's Mechanism for the investigation of the alleged use of chemical weapons. An investigation under the UN Secretary-General's Mechanism in March 1984 confirmed that Iraq was using chemical weapons on a large scale in the Iran-Iraq War. Initially, the CW agents used by Iraq were mainly sulphur mustard and the nerve agent tabun (which was the first confirmed battlefield use of a nerve agent), apparently in an attempt to stop the advances of the Iranian forces (Figure 1.4).



**Figure 1.4:** *UN Secretary General's investigation of alleged use of chemical weapons in Iran in March 1984. The inspectors are examining an unexploded Iraqi sulphur mustard bomb.*

However, as the war progressed and Iraq became more experienced in producing and deploying chemical weapons, Iraq used chemical weapons increasingly as a strategic weapon, including against Iranian non-combatants. In this context, it has been reported by the United Nations that Iraq used more than 1800 tonnes of sulphur mustard, more than 140 tonnes of tabun and more than 600 tonnes of sarin during the Iraq-Iran War. Particularly horrific examples included the use of sulphur mustard against the town of Sardasht in north-western Iran in June 1987, and the use of the nerve agent sarin against

the Kurdish village of Halabja in northern Iraq in March 1988 (Figure 1.5). The large-scale use of chemical weapons by Iraq in the Iran-Iraq war in the 1980s was a major driving force for the negotiation of the Chemical Weapons Convention.



**Figure 1.5:** *Villagers are overcome and die after exposure to sarin nerve agent while trying to flee after the chemical weapons attack on Halabja in March 1988.*

In the 1980s, 'binary' chemical weapons were developed. These contained the two key precursor chemicals of the nerve agent in separate containers within the munition, which mix and form the CW agent when the munition (typically, artillery shell, rocket, or aerial bomb) is on its way towards the target. As a means of overcoming its problems with producing stable nerve agents, Iraq developed a different binary munitions concept, in which the precursors were mixed and the munition filled shortly before it was to be used.

Chemical weapons have also been used on a small scale by non-State actors, with the most notorious of these being the sarin nerve agent attack in a Tokyo subway (in March 1995) by the Aum Shinrikyo religious cult. The attack killed 13 civilians and seriously injured more than 1,000 others (Figure 1.6).



**Figure 1.6:** *Aftermath of the sarin nerve agent attack in the Tokyo subway system in March 1995.*

On 29 April 1997, the Chemical Weapons Convention entered into force, meaning that the prohibition of the production, stockpiling, and use of chemical weapons was finally brought into effect following more than two decades of negotiations in Geneva. The Convention is implemented by the Organisation for the Prohibition of Chemical Weapons (OPCW), and with 192 States Parties, membership is now almost universal.

As of October 2015, 72,525 metric tonnes of chemical weapons stockpiles have been declared to the OPCW. Ninety percent of this stockpile has already been destroyed under strict verification by the OPCW (Figure 1.7). It is anticipated that the remaining declared stockpiles of chemical weapons in Libya, the Russian Federation, and the US will be destroyed by their respective planned completion dates of 2015, 2020, and 2023.



**Figure 1.7:** *OPCW inspectors verifying the declaration of chemical weapons prior to their destruction.*

In 2013, reports emerged of sarin attacks in Syria. This was an unprecedented challenge to the OPCW because Syria was in a state of civil war and was not a member of the Chemical Weapons Convention. This led to strong cooperation between the OPCW, the United Nations, and the World Health Organization, resulting in the creation of the OPCW-UN Joint Mission, which confirmed that sarin had been used against civilians in Syria. The largest scale chemical weapons attack occurred on 21 August 2013, when several opposition-controlled or disputed areas of Ghouta, a suburb of Damascus, were struck by rockets containing sarin. It has been reported that there were several hundreds of casualties.

Following pressure from the international community, Syria joined the Chemical Weapons Convention in September 2013 and the OPCW-UN Joint Mission subsequently facilitated the removal of Syria's declared chemical weapons under dangerous and difficult circumstances. With the destruction of the declared chemical weapons, agent, production and storage facilities, and mixing and filling equipment, Syria's chemical weapons programme is now largely dismantled. Despite the progress

made towards eliminating Syria’s chemical weapons programme, there have been a number of subsequent chemical weapon attacks in Syria using chlorine and other toxic industrial chemicals. The UN-supported OPCW fact-finding missions tasked with investigating alleged use of chlorine in Syria have confirmed such use.

While the provisions of the 1925 Geneva Protocol and the Chemical Weapons Convention did not prevent the use of chemical weapons in Syria in 2013, the roles played by the UN and the OPCW in confirming the use of chemical weapons in Syria, and in encouraging Syria to accede to the Chemical Weapons Convention and promptly destroy its chemical weapons stockpile, prevented what could have been considerably greater loss of life and suffering due to chemical weapons.

**Table 1.1:** *Information on Use of Chemical Weapons Since 1915*

<b>Conflict</b>	<b>Period</b>	<b>CW agent</b>	<b>Location</b>	<b>Casualty Estimates*</b>
World War I	1915– 1918	Chlorine Phosgene Hydrogen cyanide Sulphur mustard	Europe Middle-East	>1.3 million including >100,000 deaths
Russian Civil War	1919 –1921	Adamsite Diphenylchloroarsine Sulphur mustard	Russia	Unknown
2nd Moroccan War (Spain)	1923 –1926	Bromo ethyl ketone Chloropicrin Sulphur mustard	Morocco	Unknown
2nd Italo-Abyssinia War	1936 –1940	Chlorine 2-Chloroacetophenone Diphenylchloroarsine Sulphur mustard Phenylchloroarsine Phosgene	Abyssinia	50,000 – 150,000

Sino-Japan War (World War II)	1937 –1945	2-Chloroacetophenone Diphenylchloroarsine Hydrogen cyanide Lewisite Sulphur mustard Phosgene	Manchuria	>80,000 including >10,000 deaths
Yemeni Civil War	1963 –1967	2-Chloroacetophenone Sulphur mustard Phosgene	Yemen	>14,000
Viet Nam War	1965 –1975	2-Chlorobenzalmalonitrile	Viet Nam	Unknown
Iran-Iraq War	1980 –1988	2-Chlorobenzalmalonitrile Sulphur mustard Sarin Tabun	Iran Northern Iraq	>100,000 including >30,000 deaths >70,000 still receiving medical care
Aum Shinrikyo	1994 –1995	Sarin VX	Japan	>1,000 including 13 deaths
Syrian Conflict	2013 –2015	Sarin Sulphur mustard Chlorine	Syria	Unknown

\* Accurate casualty figures are often difficult to estimate accurately because usually chemical weapons are used in combination with conventional weapons.

### 1.1. Further reading

United Nations Secretary-General. *Chemical and bacteriological (biological) weapons and the effects of their possible use: report of the Secretary-General*. New York: United Nations; 1969.

Robinson, Julian Perry. *The rise of CB weapons. Volume I in: The problem of chemical and biological warfare*. Stockholm: Stockholm International Peace Research Institute; 1971.

World Health Organization. *Public health response to biological and chemical weapons: WHO guidance*. Geneva: WHO Press; 2004.



*The International Committee of the Red Cross in World War I: overview of activities.*

Available at: [www.icrc.org/en](http://www.icrc.org/en)

UNMOVIC Working Document, '*Unresolved disarmament issues: Iraq's proscribed weapons programmes*', New York: United Nations; March 2003. Available at:

[www.fas.org](http://www.fas.org)

Official website of the Organisation for the Prohibition of Chemical Weapons:

[www.opcw.org](http://www.opcw.org)

## **Chapter 2:**

# **General considerations in management of chemical casualties**

This chapter provides an overview of basic concepts that should be considered by medical personnel involved in the management of chemical weapons incidents. Planning and training of these personnel will be necessary for effective management of such incidents, particularly those involving a large number of chemical casualties whose arrival in surges at a medical support facility is likely to exceed its normal capacity.

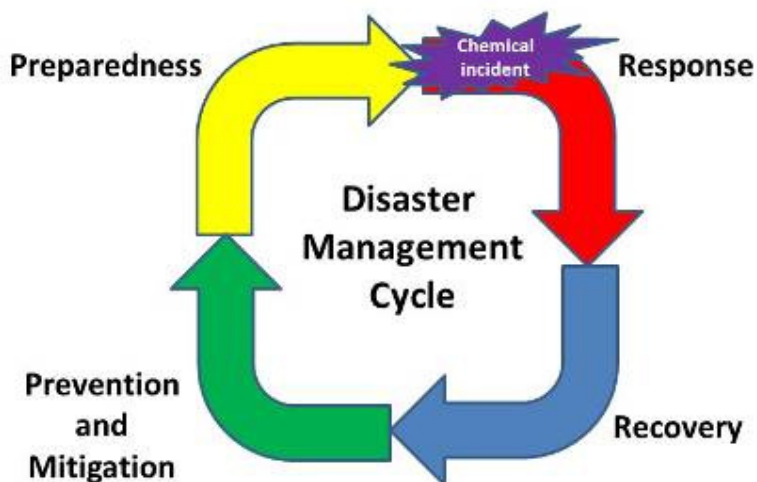
Important challenges when dealing with a chemical weapons incident include:

- Rapid agent detection and identification;
- Hazard avoidance through adequate protection and decontamination, as well as cordons to control entry to and exit from the affected area;
- Casualty decontamination, not only to reduce contact of the agent with the victim, but to avoid spreading contamination to medical treatment facilities; and
- Triage and quick medical treatment, including specific antidote therapy at the site of the incident and at the hospital level to reduce morbidity and mortality. It is important to note that medical personnel may have to deal with mass casualties, some of whom may not even have been poisoned but who may have psychogenic symptoms.

Management of a chemical incident is an ongoing process that aims to reduce or avoid potential secondary losses, assure prompt and appropriate assistance to victims, and achieve rapid and effective recovery. A basic disaster management cycle (Figure 2.1) addresses at least the following phases:

- *Prevention and mitigation:* Actions are taken before the incident to prevent or minimise consequences through assessments of hazards and vulnerabilities.
- *Preparedness:* Assessments from the first phase lead to the development of the plan to manage the chemical incident, including the acquisition of capabilities and training programmes. The plan should clearly integrate medical capabilities at the local, regional, and national levels. This may require the establishment of coordination agreements between different services and agencies so they can be integrated smoothly into the command and control system. Management plans should be as simple as possible and be clearly expressed, as complex plans may be difficult to implement.
- *Response:* The emergency plan is put into practice in a real-time event. The response phase will depend on the preparedness phase.
- *Recovery:* Finally, actions are taken to return to the pre-event situation. Such actions might include disposal of hazardous materials and remediation of the incident site, as well as further assistance to victims.

Medical management is important in all phases, although often these phases overlap and the duration of each one will vary depending on the nature and severity of the incident.



**Figure 2.1:** *Basic disaster management cycle*

### 2.1. Detection (diagnosis) and triage

When a CW incident takes place it is unlikely that, initially, first responders and medical personnel will know the identity of the agent, unless there is prior warning by intelligence or law enforcement sources. Moreover, results of unambiguous identification from laboratory identification of environmental and clinical samples will take time to reach medical personnel.

There are differing technologies available for rapid on-site detection and identification of CW agents. These include, among others:

- Ion mobility spectrometry;
- Flame photometry;
- Colourimetric/enzyme methods;
- Surface acoustic wave device;
- Photoionisation;
- Fourier transform infrared spectroscopy;

- Raman spectroscopy; and
- Gas chromatography/mass spectrometry.

All portable detection/identification devices, regardless of the technology used, sometimes yield false positives and false negatives due to their sensitivity and selectivity. Using detectors with one technology provides “provisional” detection, while using detectors of at least two different technologies provides a higher level of assurance, in particular if a colourimetric method or gas chromatography/mass spectrometry is one of the two techniques used or employed (Figure 2.2).



**Figure 2.2:** OPCW inspector using two detectors of different technologies to obtain a “confirmed” detection during training in the Czech Republic, 2008

While most portable detection equipment detects nerve and blister agents, not all of them have capabilities to detect other CW agents. Also, most of these devices were developed for military scenarios, and while available in some emergency units, they may give false responses in civilian scenarios.

For all these reasons, including a lack of availability of detection equipment in some situations, as well as lack of sufficient sensitivity and specificity, information from the signs and symptoms of poisoned patients will most likely provide the first indication of use of chemical weapons. Chapters 3 to 8 of this guidebook include information about the clinical manifestations of CW agent poisoning and triage criteria.

Medical personnel should be familiar with the main clinical signs and symptoms necessary to determine a clinical diagnosis and start the triage process, assigning priority for decontamination and medical treatment. It is important to note that the nature and timing of these clinical manifestations will vary not only with the duration and concentration of exposure, but also with the route of exposure, which should be considered in the differential diagnosis and triage process. For example, nerve agents and cyanides (blood agents) absorbed by inhalation have rapid onset of effects and need immediate treatment.

Differential diagnosis should also consider the indirect effects of chemical exposure, including heat stress from wearing protective equipment, psychological effects, and even side effects from antidotes, especially in cases where exposure to an agent has not taken place but antidotes have been administered (for example, autoinjectors with nerve agent poisoning antidotes). Differential diagnosis and triage may also be complicated in cases of mixed casualties who have both conventional and chemical injuries.

This Guide also includes information on specific antidotes for CW agent poisoning. However, the availability of antidotes will depend on local, regional and national medical doctrines, policies, and regulations. When specific antidotes are not available, therapy will be limited to supportive care.

## 2.2 Triage

In a chemical mass casualty situation medical resources will be overwhelmed. Triage is a medical decision process used to arrange patients in priority order to ensure the most effective use of limited medical resources and minimize morbidity and mortality. Triage is a dynamic process through the patient care chain used to assign priority for treatment, evacuation and decontamination.

There are different systems for chemical triage. One of the most commonly used contains four categories:

- Immediate: This category includes patients requiring emergency life-saving treatment. Treatment should not be time consuming or require numerous, highly trained personnel, and the patient should have a high chance of survival with therapy.
- Delayed: The general condition of the patients in this category permits some delay in medical treatment, although some continuing care and pain relief may be required before definitive care is given.
- Minimal: This category includes those patients with relatively minor signs and symptoms who can care for themselves or who can be helped by untrained personnel.
- Expectant: Patients in this category have a low chance of survival. Life threatening conditions of these patients will be beyond the treatment capabilities of the available medical personnel.

Table 2.1 describes chemical triage by triage category and type of agent. However, more specific triage criteria for certain CW agents can be found in relevant chapters of this guidebook.

**Table 2.1:** Triage by category and chemical agent\*

<b><i>Immediate</i></b>
<p><i>Vesicants</i></p> <ul style="list-style-type: none"> <li>• Moderate (or severe) respiratory distress</li> </ul>
<p><i>Nerve agents</i></p> <ul style="list-style-type: none"> <li>• Talking, not walking (severe distress with dyspnea, twitching, and/or nausea and vomiting); moderate to severe effects in two or more systems (for example, respiratory, gastrointestinal, muscular); circulation intact</li> <li>• Not talking (unconscious), not walking; adequate circulation</li> <li>• Not talking, not walking, not adequate circulation (if prolonged, aggressive treatment is possible; if not classify as expectant)</li> </ul>
<p><i>Lung damaging agents</i></p> <ul style="list-style-type: none"> <li>• Respiratory distress (if intense ventilatory and other support is immediately available)</li> </ul>
<p><i>Blood agents</i></p> <ul style="list-style-type: none"> <li>• Severe distress (unconscious, convulsing or postictal, with or without apnea) with adequate circulation</li> </ul>
<b><i>Delayed</i></b>
<p><i>Vesicants</i></p> <ul style="list-style-type: none"> <li>• Burns between 5% and 50% of body surface area (liquid exposure); eye injury; airway problems starting &gt;6 hours after exposure</li> </ul>
<p><i>Nerve agents</i></p> <ul style="list-style-type: none"> <li>• Patient who has survived a severe exposure, regaining consciousness, and has resumed spontaneous respiration</li> </ul>
<p><i>Lung damaging agents</i></p> <ul style="list-style-type: none"> <li>• Delayed respiratory distress (&gt;4 hours after exposure)</li> </ul>



<p><i>Blood agents</i></p> <ul style="list-style-type: none"> <li>• Patient exposed to cyanide vapour who has survived more than 15 minutes after exposure</li> </ul>
<p><b><i>Minimal</i></b></p>
<p><i>Vesicants</i></p> <ul style="list-style-type: none"> <li>• Burns in less than 5% of body surface area (liquid exposure) in noncritical areas; minor eye injury; minor pulmonary injury</li> </ul>
<p><i>Nerve agents</i></p> <ul style="list-style-type: none"> <li>• Talking and walking; mild effects (for example, miosis, rhinorrhea)</li> </ul>
<p><i>Blood agents</i></p> <ul style="list-style-type: none"> <li>• Patient exposed to cyanide vapour who has not required therapy</li> </ul>
<p><b><i>Expectant</i></b></p>
<p><i>Vesicants</i></p> <ul style="list-style-type: none"> <li>• Burns in more than 50% of body surface area (liquid exposure); severe respiratory distress</li> </ul>
<p><i>Nerve agents</i></p> <ul style="list-style-type: none"> <li>• Not talking, not walking, not adequate circulation (if prolonged, aggressive treatment is possible, classify as immediate)</li> </ul>
<p><i>Lung damaging agents</i></p> <ul style="list-style-type: none"> <li>• Moderate to severe airway injury with early onset (&lt;4 hours after exposure)</li> </ul>
<p><i>Blood agents</i></p> <ul style="list-style-type: none"> <li>• Circulation failed</li> </ul>

\* Modified from Sidell, 1997 and Tuorinsky et al., 2008.

### 2.3. Protection measures

Medical personnel are a critical resource in case of chemical attack causing a large number of casualties. As with other responders, it is important that they do not become

victims themselves. Personal protective equipment (PPE) is the first line of defence in a chemically contaminated environment. PPE comprises a respirator and protective clothing, including suitable gloves and boots. Respirators are especially important as generally CW agents have their greatest and most rapid effect via the respiratory system.

Commonly, medical personnel will deal with poisoned patients once they have been removed from the contaminated area and have been decontaminated. However, some first-responder services and agencies (for example, firefighters and law enforcement personnel) that enter the directly affected area may assign or attach medical personnel for their own support and to make an early medical assessment. In these cases PPE will prevent exposure to chemical agents through direct contact with victims' skin, mucosa, and clothing or by inhalation of a persisting vapour hazard (particularly in confined and enclosed spaces).

Medical management while using PPE will be made more difficult due to loss of vision, mobility, dexterity, and ability to communicate. Also, working with PPE increases metabolic work, which in turn increases heat production and prevents dissipation of the heat generated by the body, increasing the risk of heat stress. This may worsen in case of adverse environmental conditions like high temperatures, high humidity, and low wind velocity, which will increase sweating and rapid dehydration. Only individuals who are physically fit and have received appropriate training in PPE should intervene in incidents requiring its use.

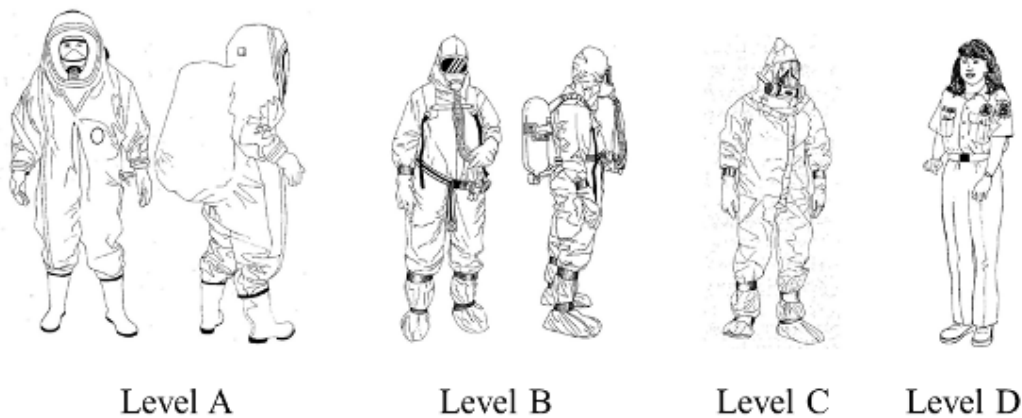
The criteria used for the classification of PPE and PPE levels vary in different countries. One of the most frequently used, included in the OPCW's assistance and protection training courses, is the US Environmental Protection Agency (EPA) four-level classification (Table 2.1 and Figure 2.3). These levels differ in respiratory and skin protection, and selection is based on the type of agent, toxicity, and concentration.

**Table 2.2:** Classification of PPE Used by the US EPA

<i>Level of Protection</i>	<i>Respiratory Protection</i>	<i>Skin Protection</i>	<i>Scenario</i>
A	Pressure-demand facepiece contained breathing apparatus (SCBA).	<ul style="list-style-type: none"> <li>Fully-encapsulated chemical-resistant suit.</li> <li>Chemical-resistant inner and external gloves and boots/shoes.</li> </ul>	<ul style="list-style-type: none"> <li>Unknown agent.</li> <li>Known agent and significant hazard of exposure (for example, high concentrations, risk of splash, immersion).</li> </ul>
B	Pressure-demand facepiece SCBA.	<ul style="list-style-type: none"> <li>Non-encapsulated hooded chemical-resistant clothing.</li> <li>Chemical-resistant inner and outer gloves and boots/shoes.</li> </ul>	<ul style="list-style-type: none"> <li>Agent known and significant respiratory protection required (but less skin protection).</li> <li>Atmosphere contains less than 19.5% oxygen.</li> </ul>
C	Full-face or half-mask purifying respirator (APR).	<ul style="list-style-type: none"> <li>Non-encapsulated hooded chemical-resistant</li> </ul>	<ul style="list-style-type: none"> <li>Agent and environment concentration known to be removed by an APR.</li> </ul>

		clothing.	<ul style="list-style-type: none"> <li>• Skin contact with known agent is non-hazardous and significant transdermal absorption does not occur.</li> <li>• Atmosphere contains at least 19.5% oxygen.</li> </ul>
• Chemical-resistant inner and outer gloves and boots/shoes.			
D	None.	<ul style="list-style-type: none"> <li>• Common work uniform.</li> </ul>	<ul style="list-style-type: none"> <li>• No known hazard.</li> </ul>

---



**Figure 2.3:** PPE levels used by the US EPA

Level A in the EPA classification should be used if the identity of the agent is unknown, or if there is risk of inhalation of a high concentration of toxic agents or risk of significant skin or mucosae damage. It consists of a fully encapsulated, vapour-tight, chemical-resistant suit, chemical-resistant inner and outer gloves, chemical-resistant

shoes or boots, and a self-contained breathing apparatus (SCBA). In case of leaks, positive pressure will allow air flow from the inside to the outside, but not from the outside to the inside.

Level B protection is used when the highest level of respiratory protection is needed (including atmospheres deficient in oxygen), but a lesser degree of skin protection is required. Thus, it includes the SCBA, but non-encapsulated suits can be used.

Level C has the same skin protection as Level B, but uses an air-purifying respirator (APR) instead of an SCBA. There are different classes and types of commercially available filters with established colour-coding systems to indicate the chemical substances against which they can be used.

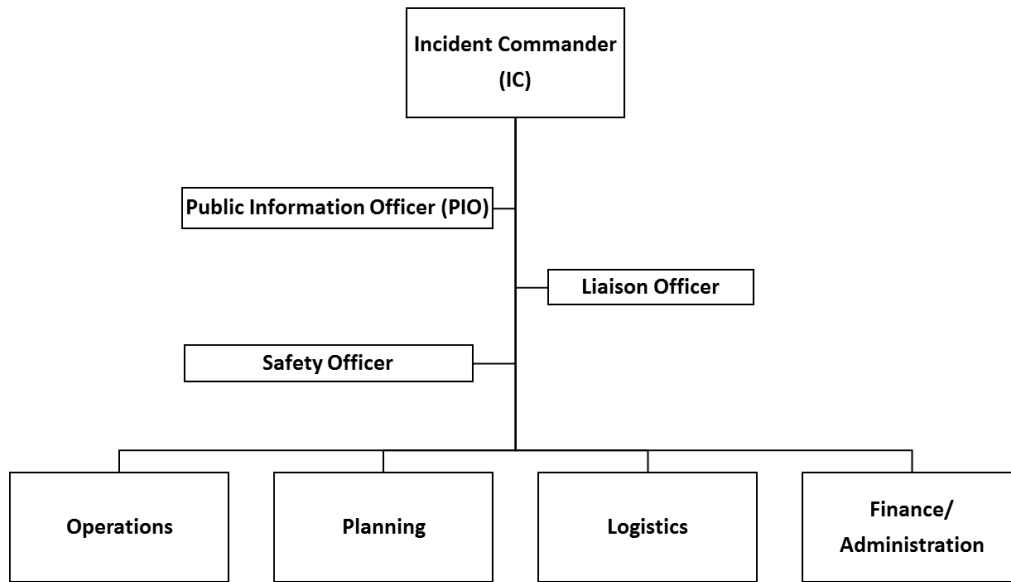
Level D is the common work uniform. Surgical masks, gowns, and gloves commonly used by medical personnel are also considered as Level D. These should not be worn on any site where respiratory or skin CW agent hazards exist.

#### **2.4. Response command and incident management**

Plans for responding to a chemical incident should include a standard and integrated procedure for multidisciplinary and multiagency teams coordinated through a single command system. In this system, the roles and responsibilities of all responders involved (medical, firefighting, law enforcement, and other emergency personnel) should be clearly specified, preferably as close as possible in agreement with the national disaster plans. Good communication among all will be essential. The system should be practised and updated based on the lessons learnt in exercises and drills.

Different nations have different management systems. For example, the Incident Command System (ICS) is used in the OPCW's assistance and protection training courses. The ICS coordinates all resources needed in the management of a chemical incident through a unified incident commander (IC).

In its basic structure the ICS includes at least four sections: operations, planning, logistics, and finance/administration (Figure 2.4). The IC is supported by a public information officer (PIO), a safety officer, and a liaison officer, who advise in media, safety, and issues involving external agencies, respectively.



**Figure 2.4:** Basic structure of the Incident Command System (ICS)

The operations section implements the IC's orders at the incident site and works together with the planning section, which performs strategic assessment and component analysis. Logistics is responsible for providing personnel, equipment, and other supplies. The finance/administration section is responsible for the acquisition of needed resources.

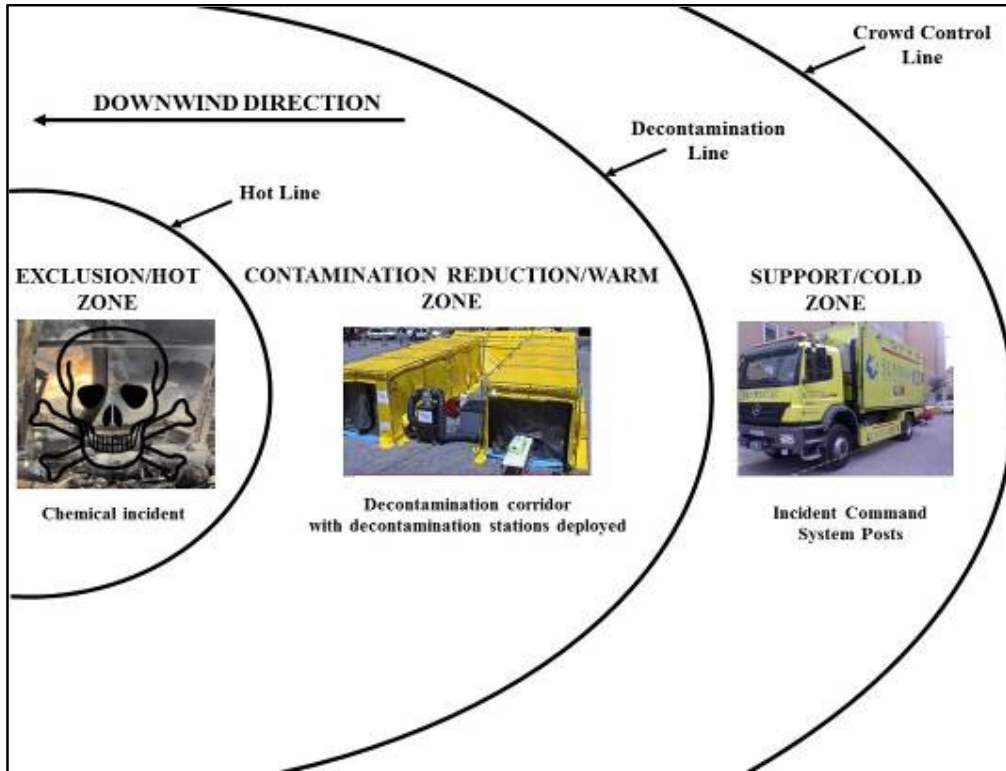
#### **2.4.1 Pre-hospital management**

To avoid spread of contamination at the site of the chemical incident, the OPCW uses the EPA recommendation to divide this area in at least three zones (Figure 2.5):

- *Exclusion zone/hot zone:* The area directly affected by the CW and which may contain vapour, liquid, or solid contamination, or a combination of these. A “hot

line” identifies the boundary between the hot zone and the warm zone.

- *Contamination reduction zone/warm zone:* The area where decontamination activities take place, which means that contamination may be present.
- *Support zone/cold zone:* An area free of contamination. A “decontamination line” identifies the boundary between the warm zone and the cold zone.



**Figure 2.5:** *Dividing zones in the CW incident area*

The management plan should specify responsibility for establishing the distances of the different zones, and law enforcement activities to control and limit access. Only firefighters, law enforcement personnel, or rescue personnel with the highest level of protection should enter the hot zone, although medical personnel may be attached. Medical personnel using PPE may also be present in the warm zone, performing first triage and emergency medical treatment to stabilise patients before they undergo

decontamination. Working in the warm zone may require Level B or C PPE, depending on the scenario, thereby limiting medical treatment of the patients. Therefore, it must be clear to all emergency services that the place of the medical personnel is in the cold zone. Only well-trained individuals under tactical supervision are allowed to act in the hot and warm zones.

Commonly, the length of the warm zone is determined based on the evolution of the situation and the length of the decontamination corridor, with all the decontamination stations available deployed. The length of the cold zone is established by the space needed by command posts, medical evacuation units, and other support personnel.

Establishing distances for the hot zone may be more complicated as it involves many interdependent variables. The management system should include experts to make such determinations and adjustments and advise the commander. As an example, the Emergency Response Guidebook 2012 (ERG2012), a tool widely used in different nations and in OPCW's assistance and protection courses, can be used as general guidance. However, ERG2012 is primarily designed for use in dangerous-goods incidents occurring on a highway or railroad and may be of limited value in other situations. Table 2.2 shows ERG2012 distances for different CW agents and toxic industrial chemicals.



**Table 2.3:** Initial isolation and protective action distances based on the 2012 Emergency Response Guidebook

Initial isolation and protective action distances						
Chemical Agent	Small spills <sup>1</sup>			Large spills <sup>2</sup>		
	Isolate <sup>3</sup> (in m)	Protect <sup>4</sup>		Isolate <sup>3</sup> (in m)	Protect <sup>4</sup>	
		Day (in km)	Night (in km)		Day (in km)	Night (in km)
Sulphur mustard	30	0.1	0.1	60	0.3	0.4
Lewisite	30	0.1	0.3	100	0.5	1.0
Sarin	60	0.4	1.1	400	2.1	4.9
Soman	60	0.4	0.7	300	1.8	2.7
Tabun	30	0.2	0.2	100	0.5	0.6
VX	30	0.1	0.1	60	0.4	0.3
Chlorine	60	0.4	1.5	500	3.0	7.9
Phosgene	150	0.8	3.2	1,000	7.5	11.0+
Diphosgene	30	0.2	0.7	200	1.0	2.4
Hydrogen cyanide	60	0.3	1.0	1,000	3.7	8.4
Cyanogen chloride	150	1.0	3.8	800	5.7	11.0+
CN	30	0.1	0.2	60	0.3	1.2
CS	30	0.1	0.6	100	0.4	1.9
BZ	60	0.4	1.7	400	2.2	8.1

<sup>1</sup>Generally, a small spill is one which involves a single small package (for example, a drum containing up to approximately 208 litres), a small cylinder, or a small leak from a large package. In case of nerve agents, vesicants and BZ, ERG2012 considers releases up to 2 kg as small spills.

<sup>2</sup>A large spill is one which involves a spill from a large package, or multiple spills from many small packages. In case of nerve agents, vesicants and BZ, ERG2012 considers releases up to 25 kg as large spills.

<sup>3</sup>The initial isolation zone defines an area surrounding the incident in which persons may be exposed to dangerous (upwind) and life-threatening (downwind) concentrations of material.

<sup>4</sup>The protective action zone defines an area downwind from the incident in which persons may become incapacitated and be unable to take protective action and/or may incur serious or irreversible health effects.

### **2.4.2 Hospital management**

Hospitals need to be integrated in the disaster management plan. This will provide adequacy of patient evacuation based not only on their proximity to the affected area, but also on their capability to receive patients, which should be continually updated during the response phase in order to maintain a balanced patient distribution. Good communication will also ensure adequate ambulance transport to suitable reception areas. Integration of all medical treatment facilities in the management system will also ensure dissemination of the identification of the CW agent, once it is conclusively verified by laboratory tests. Thus, adequate medical treatment, including antidotal therapy, can be provided.

Hospitals should also have their own emergency plans. Once activated, security personnel should control the access of people and vehicles to the hospital and direct them to the reception area. It is possible that contaminated patients may arrive by their own means, and a decontamination corridor (similar to that of the warm zone, discussed in more detail below) will have to be deployed, commonly outside the emergency department or in a previously established area. Hospital staff entering into contact with potentially contaminated patients should use PPE. Level C protection is commonly sufficient.

## **2.5 Decontamination**

The aim of decontamination is to rapidly and effectively render toxic substances harmless or to remove them from both personnel and equipment. This is achieved through physical removal and by chemical inactivation. It is especially important in cases of exposure to liquid nerve agents that rapidly penetrate the skin or to sulphur mustard, as it causes cellular damage to the skin within a very few minutes of contact. Every situation will be different, and decontamination efforts and procedures might vary depending upon the quantity and type of CW agent.

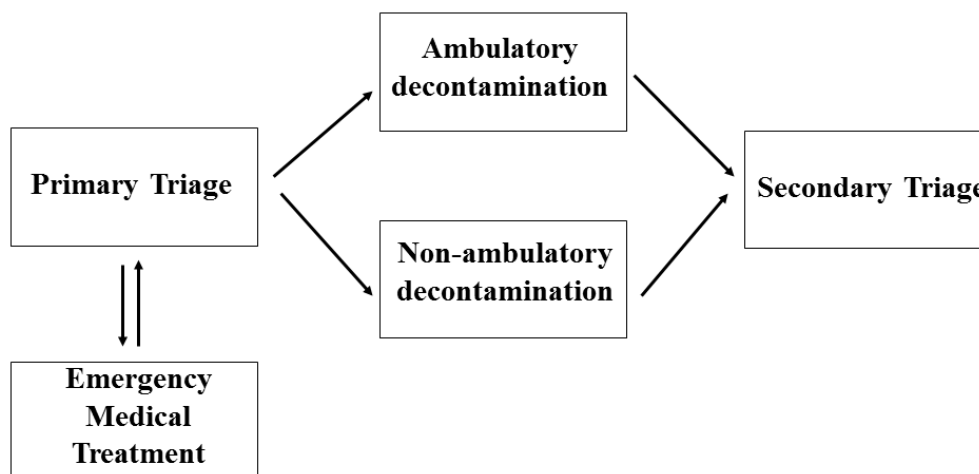
It is estimated that about 80% of decontamination takes place just by removing the clothes, as cloth fibres can trap and hold liquid agents and vapours. Removing clothing as well as jewellery and watches outside the treatment area will reduce the risk from vapour off-gassing and will increase evaporation of any liquid contaminants from the patient's skin. However, care should be taken that the process of removal does not contaminate parts of the skin that were not contaminated before.

Skin decontamination products are available commercially, but (after removing clothing) simple decontamination can be done with copious amounts of water and soap through the “rinse-wipe-rinse” technique. In the case of eye exposure, extensive irrigation with water or a 0.9% saline solution helps (after removing any contact lenses). Special attention should be paid to hair, as it may retain vapour and decrease evaporation of any liquid agent. Dry decontamination with absorbent materials (for example, Fuller's earth) of skin areas exposed to liquid agent is also very effective. In case of combined injuries, 0.9% saline solution can be used to irrigate and wash the wound area and reduce rapid agent absorption.

Casualty decontamination will prevent further ongoing absorption and will also avoid the spread of contamination to other people and facilities. Medical resources are critical in a CW scenario, and casualty decontamination before evacuation will prevent secondary contamination of medical personnel, ambulances, and facilities.

### ***2.5.1 Decontamination stations***

No person or casualty should exit the hot zone without going through the decontamination corridor. In the same manner, no person or casualty who has not gone through decontamination should enter hospitals. Figure 2.6 shows a scheme of a basic decontamination station. Level C PPE may be acceptable at decontamination stations, although it may be increased depending on the scenario. Work times must be monitored to prevent fatigue, dehydration, and heat stress, and emergency plans should establish schedules for the rotation of personnel.



**Figure 2.6:** *Scheme of a basic decontamination station*

Before or after the primary triage, casualties would go through registration, where personal information is recorded and personal belongings are separated and secured (in case they can be decontaminated and returned afterwards). Whenever possible, children and parents or accompanying adults should remain together through the decontamination process and evacuation.

Some decontamination stations include a contamination control step at the entrance if detectors are available. If the person is declared “clean” he can exit the decontamination process. However, the limitations of chemical detectors have already been discussed, and, moreover, monitoring will take time, which in case of a mass-casualties scenario would lengthen the whole decontamination process.

If medical personnel are available, a first triage can be made for assigning priority for decontamination. In case of severe casualties, an emergency medical treatment site can also be established to administer vital life support of cardiovascular and respiratory functions before going through the decontamination process. However, medical personnel will be using PPE, and unless adequate equipment and medication is available

(for example, air-filtering assisted ventilation equipment adapted for a contaminated atmosphere or antidotes in autoinjectors or prefilled syringes), only limited critical care will be provided.

Decontamination stations should have two separate lines, one for ambulatory patients who can perform the “rinse-wipe-rinse” technique by themselves or with assistance or under supervision, and a special litter decontamination lane for non-ambulatory patients. Decontamination of non-ambulatory patients is a time-consuming and labour-intensive effort. Some commercial decontamination lanes (requiring time and personnel to install) reduce this effort by using rollers to move stretchers along the lane. If available, multiple showers in gender-specific tents provide privacy.

Some decontamination stations also include a contamination control at the end of the decontamination process. Detectors are used to check whether decontamination has been effective. The limitations of contamination control have already been discussed.

Once in the cold zone, patients without clinical signs or symptoms of CW agent poisoning can be discharged, with clear advice to seek medical help in case of delayed development of symptoms (names and contact information should be registered). Patients with clinical manifestations should go through the ongoing triage process that will assign priority for therapy care at the cold zone or for evacuation.

## **2.6. Further reading**

Agency for Toxic Substances and Disease Registry. *Managing hazardous materials incidents: a planning guide for the management of contaminated patients, Vols. I, II and III*. Atlanta: Department of Health and Human Services; 2000.

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## **Chapter 3:**

### **Vesicants (blister agents)**

#### **3.1. Introduction**

Blister or vesicant agents are likely to be used both to produce casualties and to force opposing troops to wear full protective equipment. This will degrade fighting rather than kill, although very severe exposure to vesicants can be fatal. Moreover, poisoning will lead to consumption of a high volume of resources, thereby provoking a collapse of specialised branches of the health system such as burns units. Blister agents can be thickened in order to enhance persistency and contaminate terrain, ships, aircraft, vehicles or equipment.

The vesicant agents include sulphur mustard (H or HD, which refers to distilled mustard), nitrogen mustard (HN), and the arsenical vesicants such as Lewisite (L), which may well be used in a mixture with H. They also include the halogenated oximes, such as phosgene oxime (CX), whose properties and effects are very different from those of the other vesicants and are not covered in any further detail in this chapter.

Vesicants burn and blister the skin or any other part of the body surface they contact. They act on the eyes, mucous membranes, lungs, skin, and blood-forming organs (bone marrow and spleen). They damage the respiratory tract when inhaled and cause

vomiting and diarrhoea when ingested. Blister agents may also cause bone marrow suppression and have effects on other germ cells.



**Figure 3.1:** JS Sargent's classic 1918 oil painting depicting mustard gas use at Ieper during World War I.

### 3.2. Mustard agents

Sulphur mustard was used extensively in World War I (Figure 3.1) and has been used more recently in Iran and Iraq (Figure 3.2). Protection against these agents can only be achieved by a full protective ensemble. The respirator alone protects against eye and lung damage, but does not give sufficient protection against systemic effects. Extensive, slow-healing skin lesions and other effects will place a heavy burden on the medical services.

Sulphur mustard is the best known of these agents. It was first synthesised in 1822, and its vesicant properties were discovered in the middle of the nineteenth century. It was used for the first time as a CW agent in 1917 near Ieper, Belgium, from which it derives its French name (yperite). Sulphur mustard is 2,2'-di(chloro-ethyl)-sulphide. It is also known by the name "lost" in German. In the US, the symbol HD has been given to the distilled product; this abbreviation will be used in this section.



In 1935 it was discovered that the vesicant properties remained when the sulphur atom was substituted by a nitrogen atom. Thus it became possible to synthesise the nitrogen mustards with similar properties, of which there are three:




- (1) N-ethyl-2,2'di(chloroethyl)amine, (HN1).
- (2) N methyl-2,2'di(chloroethyl)amine, (HN2).
- (3) 2,2',2''tri(chloroethyl)amine, (HN3).

All of the above nitrogen mustards are alkylating agents and HN2 was introduced in 1935 as the first chemotherapeutic agent. From a military standpoint, HN3 is the principal representative of the group of nitrogen mustards and is the only nitrogen mustard likely to be used in war. HN appears to be less toxic than HD.

### ***3.2.1. Physical and chemical properties***

The physical and chemical properties of the mustard agents are compared in Table 3.1, below.

**Table 3.1:** Physical and chemical properties of mustard agents

Property	Sulphur Mustard	Nitrogen Mustard	Lewisite
Appearance	Colourless to light yellow liquid, giving off a colourless vapour	Dark coloured liquid, giving off a colourless vapour	Dark oily liquid, giving off a colourless vapour
Chemical formula	C <sub>4</sub> H <sub>8</sub> Cl <sub>2</sub> S	C <sub>6</sub> H <sub>12</sub> Cl <sub>3</sub> N	C <sub>2</sub> H <sub>2</sub> AsCl <sub>3</sub>
Structure			
Molecular weight	159.08	204.54	207.32
Density (g·cm <sup>-3</sup> ) (25°C)	1.27	1.24	1.88
Melting point (°C)	14.45	-3.7	-1.2
Boiling point (°C)	217.5	257.2	195.9
Vapour density	5.5	7.1	7.2
Vapour pressure (mm Hg) (25°C)	0.11	0.011	0.35
Volatility (mg·m <sup>-3</sup> )	92 (0°C) 610 (20°C) 910 (25°C) 2,860 (40°C)	13 (0°C) 76 (20°C) 121 (25°C) 390 (40°C)	330 (0°C) 2,500 (20°C) 3,900 (25°C) 12,000 (40°C)

### 3.2.2. Detection

Mustard agents can be detected by a variety of means. Single- and three-colour detector papers will detect liquid agent and are available for individual issue. Monitoring devices for vapour hazard and water testing kits are also available. For biomedical verification of exposure to mustard, highly specialised laboratories use

sophisticated analytical methods to determine, *inter alia*, the agent itself, metabolites, and protein adducts.

### **3.2.3. Protection**

Ordinary clothing gives little or no protection against mustard agents. The only practical preventative method is physical protection: a respirator, Level A PPE suit, gloves, and foot protection are required. Due to slow absorption of mustard by many materials, protective equipment must be changed regularly. Anti-gas barrier creams were developed in World War II, and subsequent work to develop and deploy more effective protective topical barrier creams is progressing in some NATO countries. There is no drug available to prevent the effects of mustard on the skin and the mucous membranes.

### **3.2.4. Decontamination**

Exposure to mustard is not always noticed immediately because of the latent and sign-free period that may occur after skin exposure. Recently, reactive skin decontamination lotion (RSDL) was introduced in several military forces as a product to remove or neutralise CW agents, T-2 mycotoxins, and many pesticide-related chemicals from the skin. It received clearance from the US Food and Drug Administration (FDA) and has received European CE Mark and Australian Therapeutic Goods Association clearance.

#### *a) Decontamination of mucous membranes and eyes*

The substances used for skin decontamination are generally too irritant to be used on mucous membranes and the eyes. The affected tissues should be flushed immediately with copious amounts of water. The eyes can be flushed with water or, if available, isotonic sodium bicarbonate (1.26%) or saline (0.9%).

### *b) Decontamination of the skin*

Each serviceperson is given the means for a preliminary decontamination of the skin; this is based on physical adsorption or on the combination of physical adsorption and chemical inactivation. Physical adsorption can be achieved by adsorbing powders. Practitioners that are deployed in vesicant scenarios should be equipped with RSDL.

If nothing else is available, large quantities of water can be used to dilute and flush away any remaining agent on the skin surfaces. However, this should be recognised as a far from perfect solution and may only disperse the agent over the skin if insufficient water is used.

### **3.2.5. Mechanism of action**

The exact mechanism of action is not known. However, central to many of these mechanisms is the ability of sulphur and nitrogen mustards to alkylate a very wide range of biologically important molecules. Sulphur and nitrogen mustards are bifunctional alkylating agents, and binding of agents to DNA produces a range of effects as follows:

- (1) Due to their relative instability, N7-alkylated guanine residues may be released from DNA. Upon DNA replication, the remaining apurinic sites do not provide a proper template of information, resulting in erroneous incorporation of nucleotides. This may lead to mutations and synthesis of non-functional proteins.
- (2) After damage to DNA, cellular repair mechanisms may not be error free. These processes thus may also give rise to erroneous DNA replication.
- (3) Crosslinks, in particular interstrand crosslinks between two guanines for example, may play an important role in the cytotoxicity of the sulphur and nitrogen mustards. They inhibit the DNA replication process.

### **3.2.6. Toxicity**

Three distinct levels of biological action can be discerned following exposure to mustards: cytostatic, mutagenic, and cytotoxic effects. The possibility that some effects might be due to reactions with cellular membranes or critical enzymes cannot be dismissed. The actions of mustards partly resemble those of ionising radiation and, as such, mustards have been referred to as radiomimetic compounds. Actively proliferating cells are affected most; thus basal epidermal cells, the haemopoietic system, and the mucosal lining of the intestine are particularly vulnerable.

### **3.2.7. Signs and symptoms**

#### *a) Eyes*

The eyes are more susceptible to mustard than either the respiratory tract or the skin. Mild effects may be seen within approximately 1 hour following exposure to concentrations barely perceptible by odour. A latent period of 4 to 12 hours follows mild exposure, after which there is lachrymation and a sensation of grit in the eyes. The conjunctivae and the lids become red and oedematous. Serious exposure irritates the eyes after 1 to 3 hours and produces severe lesions.

#### *b) Skin*

The hallmark of sulphur mustard exposure is latency—a symptom- and sign-free period for some hours after exposure. The duration of this period and the severity of the lesions is dependent upon the level and type of exposure, environmental temperature and, probably, on the individual. High temperature as well as hydrated, thin or delicate, and occluded skin are associated with more severe lesions and shorter latent periods for a given dose. Some people are markedly more sensitive to mustard than others. Burns may be the result of either vapour or liquid exposure.



**Figure 3.2:** *a. and b. Iranian casualties showing large, fluid-filled blisters, the characteristic acute manifestation of sulphur mustard exposure of the skin. c. A large sulphur mustard burn of the thigh following rupture of several large blisters and the early development of superficial infection of the resulting necrotic ulcers. d. A partially healed mustard burn of the forearm, showing the typical areas of peeling epidermis surrounded by zones of hypo- and hyper-pigmentation.*

The sequence of skin changes normally seen is as follows:

- (1) *Erythema (2 to 48 hours after exposure)*. This superficial reddening of the skin may be very striking and reminiscent of scarlet fever. Slight oedema of the skin may occur. Itching is common and may be intense. This sequence is reminiscent of that seen in sunburn.
- (2) *Blistering*. Erythema is followed by the development of numerous small vesicles which may coalesce to form larger blisters. The blisters are not painful per se, though they may be uncomfortable and feel tense. Blisters at points of flexure— anterior aspects of elbows and posterior aspects of knees—can seriously impede

movement. Mustard blisters are delicate and may be ruptured easily by contact with bed linen or bandages or during transport of casualties. Crops of new blisters may appear as late as the second week following exposure. The blister fluid is not vesicant and does not produce secondary blistering.

- (3) *Deep burning leading to complete epidermal loss.* This is particularly likely to occur on the eyelids, penis, and scrotum since the epidermis in these sites is particularly thin, naturally moist, and often occluded.

The regeneration of these tissues is very slow, taking from several weeks to several months, much longer than the time required for the restoration of skin destroyed by other physical means or by caustic compounds. Healing may result in scarring and fragile skin which may be easily damaged by trauma, but the overall prognosis of these lesions is better than comparable thermal burns.

The systemic fluid derangement seen as a consequence of these injuries is appreciably less than for thermal burns and, therefore, the overall outcome is better.

#### *c) Respiratory tract*

Mustard attacks all the mucous membranes of the respiratory tract. After an average latent period of 4 to 8 hours (derived from a dose-dependent range of 2 to 48 hours), mustard irritates and congests the mucous membranes of the nasal cavity and the throat, as well as the epithelium of the trachea and large bronchi.

Symptoms start with rhinorrhoea, burning pain in the throat, and hoarseness of the voice. This pain may make the patient reluctant to cough. A dry cough gives way to copious expectoration. Airway secretions and fragments of necrotic epithelium may obstruct the airways; rales and reduced air entry can be detected by auscultation. There is pronounced dyspnoea. The damaged lower airways become infected easily, predisposing to bronchopneumonia after approximately 48 hours.

#### *d) Gastrointestinal tract*

Ingestion of contaminated food or water will lead to symptoms that include nausea, vomiting, pain, diarrhoea, and prostration. These features may make casualties reluctant to eat. Hypovolaemic shock may occur from the loss of fluids and electrolytes from prolonged vomiting and diarrhoea.

#### *e) Systemic action*

Mustards that are systemically absorbed by any route, including severe skin exposure, may cause signs similar to those of irradiation: headache, gastrointestinal pain, nausea, vomiting, leucopenia, and anaemia. The development of severe leucopenia or aplastic anaemia makes survival unlikely.

### **3.2.8. Treatment of mustard lesions**

#### *a) Prophylaxis*

There is no drug therapy available for preventing the effects of mustard.

#### *b) Therapy*

There is no specific therapy available for the treatment of mustard lesions. The aim of therapy is to relieve symptoms, prevent infections, and promote healing.

#### *c) Eye lesions*

The ocular effects of mustard are very painful. Use of local analgesics may increase corneal damage and are not recommended; systemic analgesics (narcotics) should, therefore, be used as required. Secondary infection is a serious complication and increases the amount of corneal scarring.

To prevent infection, appropriate anti-bacterial preparations should be used. When the lesion proves more serious (for example, blistering of the eyelids or blepharospasm), the anti-bacterial preparation should be applied at more frequent intervals. Patients with



corneal lesions should receive mydriatics to prevent adhesions between the iris and cornea.

More severe injuries will cause enough oedema of the lids, photophobia, and blepharospasm to obstruct vision. This alarms the patients. To allay their fears, the lids may be gently forced open to assure them that they are not blind.

#### *d) Respiratory tract lesions*

Mild respiratory tract injury, with hoarseness and sore throat only, usually requires no treatment. Cough may be relieved by codeine. Laryngitis and tracheitis may be treated symptomatically with steam or sterile cool mist inhalations. If more severe respiratory tract injury is suspected, hospitalisation may be advisable. If a bacterial pneumonia occurs, isolation of the specific organisms with their antibiotic sensitivities should be performed, then antibiotic therapy can be targeted. In cases of overwhelming exposure, severe diffuse lung damage may result and such casualties may need supported ventilation.

#### *e) Skin lesions*

It is important to ensure that no remaining contamination is present before commencing treatment. The skin becomes red and itches intensely. This itching can be diminished by local applications of cooling preparations such as calamine lotion, corticosteroid preparations, or silver sulphadiazine cream.

Severe erythema around the genitalia may become quite painful, and weeping and maceration may ensue. Often, treatment with exposure of the area is desirable, and care must be taken to ensure that secondary infection of tissue does not occur. Infection is the most important complicating factor in the healing of mustard burns.

There is no consensus on the need to de-roof blisters or on the optimum form of treatment (open or covered, dry or wet). Once blisters have broken, it is best to remove

their ragged roofs and cover with sterile dressings as soon as possible. Routine wound inspection aids in the early detection of and institution of appropriate therapy for any complicating bacterial infections. Analgesics should be given as required. Skin grafting may be required to effect early closure of the burn injury and has been shown to produce a good cosmetic outcome.

In a recent review on the casualties from the Iran-Iraq conflict, it appeared that the healing process and the final outcome were more dependent on the severity of the initial lesion than on the treatment applied.

#### *f) Systemic effects*

Every effort should be made to maintain adequate metabolic status and to replace loss of fluids and electrolytes. Infection should be treated promptly and vigorously. The use of colony-stimulating factors can be recommended to shorten the duration of leucopenia.

### **3.2.9 Triage**

Patients arriving directly from the scene of a potential exposure (within 30 to 60 minutes) will rarely show any signs or symptoms. As a rough guide, the sooner after exposure that symptoms occur, the more likely the patient has sustained a severe exposure and, in the absence of immediate decontamination, the more likely they are to progress and become severe.

The following is a guide to prioritisation of casualties based on their presenting signs and symptoms.

#### *Immediate*

Mustard casualties, especially those with eye involvement, are often classified as immediate for the purposes of decontamination. Immediate decontamination within 2 minutes of exposure is an important primary measure that will reduce the severity of later signs and symptoms and decrease the damage to the tissues. Casualties with mustard

burns over 50 % or more of the body surface area or burns of a lesser extent coupled with more than minimal pulmonary involvement should initially have a guarded outcome and may require intensive care for weeks to months, potentially in an aseptic environment.

#### *Delayed*

Most mustard casualties are generally classified as delayed for medical attention.

#### *Minimal*

These casualties have a very small lesion (< 5 % of body surface area in a non-critical area and/or minor eye or respiratory symptoms).

#### *Expectant*

At less than 4 hours post exposure, casualties with burns over 50 % or more of the body surface area secondary to mustard exposure and/or lower respiratory signs (dyspnea) should be regarded as expectant, particularly in the absence of intensive care medical intervention.

### **3.2.10 Course and prognosis**

The great majority of mustard casualties survive. Resolution of specific problems can be difficult to predict but the following is a guide:

- (1) *Eye lesions*: Most are resolved within 14 days of exposure.
- (2) *Skin lesions*: Deep skin lesions may be expected to heal in up to 60 days.  
Superficial lesions heal in 14 to 21 days.
- (3) *Upper respiratory tract lesions*: It is very difficult to define a time course for complete recovery. Patients from the Iran-Iraq conflict were often discharged whilst still coughing and complaining of expectoration. Lung-function tests on patients with purely upper respiratory tract lesions were usually normal on discharge. Patients with parenchymal damage often showed an abnormal pattern on lung-function testing.

### 3.2.11 Long-term effects of sulphur mustard poisoning

The long-term effects of sulphur mustard poisoning may be divided into three groups:

- (1) Prolonged psychological manifestations including post-traumatic stress disorder (PTSD), chronic depression, loss of libido, and anxiety may occur in personnel exposed to mustard agents.
- (2) Local effects of sulphur mustard exposure may include :
  - Visual impairment, although permanent blindness is extremely rare.
  - Scarring of the skin.
  - Chronic obstructive pulmonary disease, including chronic bronchitis, emphysema, and reactive airway disease.
  - Bronchial stenosis.
  - Gastrointestinal stenosis with dyspepsia after ingestion of agent.
  - Increased sensitivity to mustard.
- (3) Sulphur mustard is a known carcinogen. A study of American soldiers exposed to sulphur mustard during World War I revealed an increased incidence of lung cancer (and chronic bronchitis) compared to soldiers who had sustained other injuries. A study of British workers involved in the production of sulphur mustard during World War II revealed no increase in deaths due to cancer amongst those who had died since 1945, but did show an increase in the prevalence of laryngeal carcinoma amongst those still alive.

Although there is no specific treatment for long-term complications of sulphur mustard poisoning, the appropriate clinical management of the complications in the respiratory system, skin, and eyes remains essential.

The respiratory complications are likely to vary from one patient to another due to confounding factors such as overall health status and pre-existing disease as well as

external factors such as the duration and frequency of the initial exposure, emergent and follow-up medical care, co-exposures and smoking. Therefore, decisions concerning the medical management of complications have to be made on a case-by-case basis.

N-acetyl cysteine (NAC) as a mucolytic and antioxidant agent is effective in the treatment and control of chronic lung conditions due to sulphur mustard. NAC has been shown to improve pulmonary function tests (PFT), reduce the incidence of bronchial infections and exacerbations, and improve the overall quality of life of these patients. Inhaled bronchodilators such as salbutamol and inhaled corticosteroids like beclomethasone and fluticasone are required for treatment of the obstructive and restrictive patterns of chronic lung disease. The macrolide antibiotics such as Clarithromycin and Azithromycin are effective in reducing mustard-induced overproduction of pro-inflammatory cytokines and mediators as well as improving the degenerated chemotactic and phagocytotic functions of monocytes.

Local emollients and systemic antihistamines can improve skin dryness and reduce itching. In addition, topical corticosteroids are currently the most administered medications for chronic skin lesions and pruritus due to mustard poisoning.

In cases of chronic keratitis, the following should be considered, depending on severity: preservative-free artificial tears, therapeutic contact lenses, immunosuppressive drugs such as azathioprine, temporary or permanent punctual occlusion, as well as blepharorrhaphy, tarsorrhaphy, and other specialist surgical treatments. A limited course of topical steroids may be used to control recurrent episodes of superficial inflammation, keratitis, or limbal inflammation. Ophthalmological consultation is required in complicated cases of chronic eye injuries.

### **3.3. Arsenical vesicants (Lewisite)**

The arsines possessing the  $-\text{AsCl}_2$  group are endowed with vesicant properties. Of these, Lewisite is the best known and the most characteristic. Initially, preparations contained considerable impurities, but at the end of World War I it was purified in the US (but not used operationally). Lewisite is 2-chlorovinyl-dichloroarsine,  $\text{ClCH}=\text{CHAsCl}_2$ .

#### **3.3.1. Detection**

The detection of Lewisite is facilitated by the fact that it forms coloured products with many reagents. Draeger™ tubes are available that react with organic arsenicals. Detectors are available for use in the field.

#### **3.3.2. Protection**

Ordinary clothing gives little or no protection against Lewisite. A respirator, Level A PPE suit, gloves, and foot protection are therefore required.

#### **3.3.3. Decontamination**

The decontamination procedure is the same as for mustard.

#### **3.3.4. Signs and symptoms**

##### *a) Eyes*

Liquid arsenical vesicants cause severe damage to the eye. On contact, pain and blepharospasm occur instantly. Oedema of the conjunctivae and lids follows rapidly and closes the eye within an hour. Inflammation of the iris is usually evident by this time. After a few hours, the oedema of the lids begins to subside, but haziness of the cornea develops and iritis increases.

Liquid arsenical vesicants instantly produce a grey scarring of the cornea, like an acid burn, at the point of contact. Necrosis and separation of both bulbar and palpebral conjunctivae may follow very heavy exposure. All injured eyes are susceptible to secondary infection. Mild conjunctivitis due to arsenical vesicants heals in a few days without specific treatment. Severe exposure may cause permanent injury or blindness.

*b) Skin*

Liquid arsenical vesicants produce more severe lesions of the skin than liquid mustard. Full-thickness injury to the skin occurs, and burns may penetrate to connective tissue and muscle, causing greater vascular damage and more severe inflammatory reaction than in mustard burns. In large, deep arsenical vesicant burns, there may be considerable necrosis of tissue and gangrene.

*c) Respiratory tract*

The vapours of arsenical vesicants are so irritating to the respiratory tract that conscious casualties will immediately try to escape or put on a mask to avoid the vapour. The respiratory lesions are similar to those produced by mustard except that in the most severe cases, pulmonary oedema may be accompanied by pleural effusion.

*d) Systemic effects*

Liquid arsenical vesicants on the skin and inhaled vapour are absorbed systemically and may cause systemic poisoning. A manifestation of this is a change in capillary permeability; there may be loss of sufficient fluid from the bloodstream to cause haemoconcentration, shock, and death.

### 3.4 Treatment of Lewisite lesions

An antidote for Lewisite is dimercaprol (2, 3-dimercapto-propanol,  $\text{CH}_2\text{SH}-\text{CHSH}-\text{CH}_2\text{OH}$ ). It is known as British anti-Lewisite (BAL). Due to its toxicity it can only be used locally. BAL is not used by all NATO nations. A water soluble dimercaprol analogue is 2,3-dimercapto-1-propanesulphonic acid (DMPS, Dimaval®), which is licensed and in clinical use as a chelator in heavy metal poisoning. This is recommended as first-line systemic therapy in Lewisite poisoning.

#### *a) Eyes*

Dimercaprol eye ointment may diminish the effects of Lewisite if applied within 2 to 5 minutes of exposure. In severe cases, the systemic use of morphine may be necessary for control of pain.

#### *b) Skin*

BAL ointment may be applied to skin exposed to Lewisite before actual vesication has begun, but application after vesication also has benefit. BAL ointment is spread on the skin in a thin film and allowed to remain in situ for at least 5 minutes. Occasionally, BAL ointment causes stinging, itching, or urticarial weals. This condition lasts only an hour or so and should not cause alarm. Mild dermatitis may occur if BAL ointment is frequently applied on the same area of skin (this property precludes its use as a protective ointment). Dimercaprol is chemically incompatible with silver sulphadiazine and the two should not be used together.

The treatment of the erythema, blisters, and denuded areas is identical to that for similar mustard lesions. A severe full-thickness burn involving a large surface area is similar to a thermal injury and must be managed by intravenous fluid replacement to avoid hypovolaemic shock.



*c) Treatment of systemic effects*

The following are indications for the use of systemic treatment:

- (1) Cough with dyspnoea and frothy sputum, which may be blood-tinged and other signs of pulmonary oedema.
- (2) Skin burn the size of the palm of the hand or larger, caused by a liquid arsenical blister agent that was not decontaminated within the first 15 minutes.
- (3) Skin contamination by a liquid arsenical vesicant covering 5% or more of the body surface, in which there is evidence of immediate skin damage (grey or dead-white blanching of the skin), or in which erythema develops over the area within 30 minutes.

The systemic dosing with 2,3-dimercapto-1-propanesulphonic acid (DMPS) or meso-dimercaptosuccinic acid (DMSA) has to be carefully adjusted to the severity of poisoning. A suggested regimen for severe poisoning of adults is:

- (1) Day 1: 1 ampoule DMPS i.v. every 3 to 4 hours (1.5 to 2.0 g DMPS per day)
- (2) Day 2: 1 ampoule DMPS i.v. every 4 to 6 hours (1.0 to 1.5 g DMPS per day)
- (3) Day 3: 1 ampoule DMPS i.v./i.m. every 6 to 8 hours (0.75 to 1.0 g DMPS per day)
- (4) Day 4: 1 ampoule DMPS i.v./i.m. every 8 to 12 hours (0.5 to 0.75 g DMPS per day)

On the following days, in accordance to the clinical condition, administer 1 to 3 ampoules per day or switch to oral administration.

Maintenance of metabolic status and replacement of fluids and electrolytes is important, particularly in the case of hypovolaemic shock complicating severe exposure. The specific haematological, hepatic and renal effects arising from systemic poisoning by arsenical compounds such as Lewisite may require specialist and possibly intensive medical management.

### 3.4.1. Course and prognosis

The long-term effects of exposure to Lewisite are unknown. Burns severe enough to cause shock and systemic poisoning are life-threatening. Even if the patient survives the acute effects, the prognosis will be guarded for several weeks.

### 3.5 Further reading

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## Chapter 4:

### Nerve agents

*“... Eyes and head were beginning to hurt, ... next to the puddle sat an immobile old man, he was already dying, ... on the platform, several dozen people had either collapsed or were on their knees unable to stand up, ... one man was thrashing around on the floor like a fish out of water, ... others staggered up the stairs...”*

*Several minutes after a pool of oily water with an offensive smell had appeared on the floor, commuters panicked and fled the Tokyo subway train. Time, April 3, 1995.*

The designation “nerve agent” is used to denote organophosphorus (OP) compounds that are highly toxic at small dosages. It is an allusion to the mode of action of these substances, which consists essentially of a disruption of nerve impulse transmission.

#### 4.1. Physical and chemical properties

Currently, two families of nerve agents are important for military purposes: the G-series agents, consisting of alkyl esters of methylphosphonofluoridic acid or of dialkylphosphoramidocyanidic acid, and the V-series agents, consisting of alkyl esters of S-dialkylaminoethylmethylphosphono-thiolic acid. Theoretically, these two families

include several hundred different chemical substances. The chemical and common names of some of the weaponised G and V agents are provided in Table 4.1.

**Table 4.1:** *G- and V-series agents*

<b>Chemical Substance</b>	<b>Common Name</b>
O-ethyl N,N-dimethylphosphoramidocyanidate	Tabun, GA
O-isopropyl methylphosphonofluoridate	Sarin, GB
O-1,2,2-trimethylpropyl methylphosphonofluoridate	Soman, GD
O-cyclohexyl methylphosphonofluoridate	Cyclohexyl sarin, GF
O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothioate	VX

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

**Table 4.2:** *Physical properties of G- and V-series agents*

<b>Agent</b>	<b>Melting Point °C</b>	<b>Boiling Point °C</b>	<b>Vapour Density (compared to air)</b>	<b>Vapour Pressure mm Hg at 20°C</b>
Tabun	-49	246	5.6	0.036
Sarin	-56	147	4.86	2.10
Soman	-80	167	6.3	0.27
VX	-20	300	9.2	0.00044

Tabun, sarin and soman are quite lipophilic and volatile, whereas thickened soman and VX may be quite persistent in the environment, depending on temperature. VX represents a serious persistent hazard.

Because of these characteristics, G agents are primarily designed to act via inhalation, while V agents act primarily via penetration through the skin. They may, however, be absorbed through any epithelial cell layer, the respiratory and gastrointestinal tracts, as well as conjunctivae. The route through which absorption is most rapid and complete is the respiratory tract. Aerosolised V-series agents might break through personal semipermeable, protective cloths.

Military-type, semi-permeable, active-carbon-containing protective clothing and a full-face gas mask with an appropriate filter protect substantially against nerve agents. Most armies have developed effective decontamination procedures of skin, equipment, and material using neutralising, active chemicals such as chloramine solutions, or neutral adsorbing powders such as Fuller's earth.

## **4.2. Toxicological properties and mechanism of toxicity**

Chemically and toxicologically, nerve agents are similar to many of the commercial OP insecticides. They phosphorylate a serine hydroxyl group in the active site of the enzyme acetylcholinesterase, rendering the enzyme inactive. This results in accumulation of acetylcholine at muscarinic and nicotinic receptors in effector organs, and causes enhancement and prolongation of cholinergic effects as well as depolarisation blockade at muscles.

Spontaneous dephosphorylation of the enzyme occurs slowly and does not influence clinical symptoms. In some cases, especially in soman poisoning, aging of acetylcholinesterase with irreversible dealkylation of the enzyme-OP complex has to be taken into account. Restoration of activity without therapy becomes dependent upon fresh synthesis of new acetylcholinesterase.

## **4.3. Clinical manifestations of exposure**

Signs and symptoms of nerve agent poisoning are the result of enhanced stimulation of sympathetic and parasympathetic ganglia and effector organs, enhanced stimulation followed by depolarisation blockade at the neuromuscular junction, and of stimulation of the cholinergic system in the central nervous system, followed by depression. In the early phase of poisoning, orthosympathetic symptoms might occur before the parasympathetic symptoms dominate the cholinergic crisis.

**Table 4.3:** *Signs and symptoms of nerve agent poisoning\**

<b>Receptor</b>	<b>Target</b>	<b>Signs and Symptoms</b>
Muscarinic	Glands	
	Conjunctival mucosa	Hyperaemia
	Nasal mucosa	Rhinorrhoea, hyperaemia
	Bronchial mucosa	Bronchorrhea, bronchoconstriction, dyspnoea
	Sweat	Sweating
	Lacrimal	Lacrimation
	Salivary	Salivation
	Smooth muscle	
	Iris	Miosis, dim vision
	Ciliary muscle	Failure of accommodation, blurring of vision, frontal headache
	Gut	Nausea, vomiting, abdominal cramp, diarrhoea
	Bladder	Frequent, involuntary micturition
	Heart	Bradycardia, rhythm abnormalities
Nicotinic	Autonomic ganglia	Pallour, tachycardia, hypertension
	Skeletal muscle	Muscular twitching, fasciculation, weakness, paralysis
Central	Central nervous system	Giddiness, anxiety, restlessness, headache, tremor, confusion, failure to concentrate, excessive dreaming, convulsions, unconsciousness, respiratory depression

\* Slightly modified from Grob, 1963 and Marrs et al., 1996.

The time course of the appearance of signs and symptoms varies with the degree and route of absorption and the respective nerve agent. Overlapping of signs and symptoms may occur and aggravation during ongoing poisoning is possible.

Mild to moderate exposure to nerve agent vapour may result in local effects such as miosis, blurred vision, and hypersecretions. Bronchoconstriction and respiratory distress may appear before pronounced symptoms involving the gastrointestinal tract develop.

Small to moderate dermal exposure to liquid nerve agent produces increased sweating and muscular fasciculations at the site; nausea, vomiting, diarrhoea, and generalised weakness may be more marked. For V-type agents a delay of symptoms of several hours has to be taken into account.

Large-dose exposures will rapidly produce loss of consciousness, convulsions, flaccid muscle paralysis, and respiratory and circulatory failure. Exposure to several times the lethal vapour concentration of a nerve agent would probably be fatal within several minutes to half an hour. Nearly instantaneous death has been observed during what was, most probably, a sarin attack on the city of Halabja during the Iran-Iraq war in 1988. Vapour concentrations that were just lethal would probably result in death within 1 to a few hours after exposure. In a murder case where VX was applied on the skin, it took several hours before the victim died.

When exposure stops, patients may not develop the full clinical picture and may slowly recover. The effects of sarin last from several hours to several days depending on the severity of the exposure.

Inhibition of acetylcholinesterase and butyrylcholinesterase in blood provide a biological marker of poisoning. Commercial kits for pre-clinical testing of both enzymes are on the market and are recommended to be included in the standard equipment of medical chemical defence forces. Moreover, determination of individual normal values



of red blood cell acetylcholinesterase, prior to deployment, appears rational in order to enable assessment of low-dose exposure. However, testing must not delay antidote treatment.

#### **4.4 Triage**

The variety of clinical pictures observed after the Tokyo sarin exposure (see start of this chapter) indicate that a severity grading, developed in acute organophosphorus insecticide poisoning, may also be applied in nerve agent casualties. Because of differences in dose dependent elimination from the body, however, clinical signs and symptoms may evolve more rapidly in nerve agent than in insecticide poisoning.

The establishment of treatment priorities, based on severity grading, becomes important in situations with a large number of casualties and limited resources.

The following is a guide to prioritisation of nerve agent casualties based on their presenting signs and symptoms:

##### **Immediate**

- A patient who presents with severe multisystem signs and symptoms, who is conscious but unable to walk or unconscious but with adequate circulation, is classified as *immediate*.

##### **Delayed**

- A patient recovering from severe exposure or antidote therapy who presents with diminished secretion and improved respiration but unable to walk is classified as *delayed*.

##### **Minimal**

- A patient who presents with limited signs and symptoms, who is conscious and able to walk is classified as *minimal*.

## **Expectant**

- An unconscious patient who presents severe multisystem signs and symptoms, convulsions, and failing circulation and/or respiration is classified *expectant*. Only if adequate treatment resources are available, such patient can be classified as *immediate*.

### **4.5. Pre-hospital management**

Most importantly, rescuers and medical caregivers must protect themselves from contamination and casualties should rapidly be removed from the source of contamination and decontaminated (see Chapter 2).

Therapy based on the injection of an anticholinergic drug, an anticonvulsant, and an oxime should start as soon as possible. A possible dosing scheme includes a single ComboPen® autoinjector (containing atropine and an oxime) followed, if symptoms persist after 10 minutes, by a single AtroPen® autoinjector (containing atropine). If symptoms still persist after an additional 10 minutes, a second AtroPen® autoinjector may be administered.

Until the patient has been evacuated and decontaminated, treatment may require special equipment, drills, and drug delivery systems for intramuscular administration. If respiration is severely impaired, death may occur in a matter of minutes unless an effective method of artificial respiration (taking into account an initial high resistance in the airways and a possible vapour hazard from the contaminated environment) is begun immediately and maintained continuously until spontaneous respiration is resumed. Medical countermeasures like intubation or intravenous fluids in a hot zone bear the risk of additional contamination and should be kept at a minimum.

## **4.6. Decontamination**

Decontamination should be performed as soon as possible. For immediate spot decontamination, RSDL (reactive skin decontamination lotion) or other decontaminants should be used. In any case, before admission to a hospital, clothes should be removed and discarded, and exposed skin should be decontaminated to avoid cross-contamination of medical personal. If decontamination solutions or lotions are not available, copious amounts of water and soap should be used. Eyes should be rinsed with physiological saline or, if not available, with tap water.

## **4.7. Hospital management**

### **4.7.1. Anticholinergic drugs**

Anticholinergic drugs constitute a first choice of symptomatic drug therapy. Atropine sulphate, an antimuscarinic agent, blocks the parasympathetic, muscarinic symptoms (see Table 4.3). Following a (loading) dose of 2 mg, intramuscularly or intravenously, several dose regimens have been proposed in adults and especially in children. In children, dosing has not been well studied. Atropine dose required is based on the severity of intoxication and patient's response. In mild OP intoxication we could start with 2 mg, in moderate with 5 mg and in severe with 10 mg atropine and continue until achieving dryness of secretion (mild to moderate atropinisation) which is the goal of atropine treatment. However, in mild to moderate OP poisoning, example is given in table 4.4.

**Table 4.4** *Atropine sulphate dose regimens proposed in mild to moderate organophosphorus poisoning for adult and paediatric patients.*

	Loading dose	Maintenance dose till full atropinisation
adult	2 mg	0.5 – 2 mg/h
	2 mg	doubling the dose every 5 minutes (2, 4, 8, 16, 32 mg)
Children	0.01–0.03 mg/kg 0.1 mg/kg	
7-18 kg	0.5 mg	doubling the dose (or tripling) every 5 minutes
19-40 kg	1 mg	doubling the dose (or tripling) every 5 minutes

Titration of atropine in the individual patient has to be carried out on the basis of the most relevant effects for a favourable clinical outcome, i.e. decrease in bronchial constriction and secretions as judged by less dyspnoea and no rales in auscultation, and blood gas analysis. Heart rate changes are less important but easier to follow, and a mild tachycardia of 80 beats or more per minute should be maintained.

In overdose, atropine can cause urinary retention, stoppage of peristalsis, hallucinations, ataxia, tachycardia, dry mouth and dilated pupils.

#### **4.7.2. Oximes**

Oximes, which are acetylcholinesterase reactivators, constitute a causal therapy. In OP pesticide poisoning, most clinical experience has been gained with pralidoxime chloride (2-PAM Cl, Protopam chloride<sup>®</sup>), pralidoxime methanesulphonate (P2S) or methylsulphate (Contrathion<sup>®</sup>), and obidoxime chloride (Toxogonin<sup>®</sup>). More recently HI-6 (asoxime chloride) has been introduced into clinical treatment in some countries.

These agents relieve the important symptom of skeletal neuromuscular blockade and the peripheral parasympathetic symptoms, but they poorly penetrate into the central nervous system.

Very little clinical experience has been gained in the treatment of nerve agent poisoning in humans. In order to be effective, especially in the case of soman poisoning, oximes should be administered very soon after exposure because of the aging of the enzyme-OP complex that becomes in time irreversibly blocked.

Oximes should be administered as a loading dose followed by a maintenance dose. However, the status of licensing of oximes in different countries has to be taken into account. As for atropine, several dose schemes have been proposed. Differences between them are due to differences in opinion regarding oxime plasma target concentration, the therapeutic concentration. Table 4.5, setting forth a possible dose scheme for an adult person, can be used as a guide.

As for atropine, oxime dosing in children has not been well studied. Doses of one-third to two-third of the adult dose have been proposed.

*Table 4.5: Loading doses and infusion rates for oxime administration in adults to gain respective plasma target concentrations\* (Eyer, 2003)*

<i>Oxime</i>	<i>Plasma target concentration in mg/L**</i>	<i>Loading dose in mg for an adult person</i>	<i>Daily dose in mg for an adult person</i>
<i>Pralidoxime</i>	<i>14</i>	<i>1000</i>	<i>12000</i>
<i>Obidoxime</i>	<i>4</i>	<i>250</i>	<i>750</i>
<i>HI-6</i>	<i>10</i>	<i>500</i>	<i>2000</i>

\* Eyer, 2003

\*\* based on theoretical considerations to achieve a sufficient reactivation. Safety data for the high concentration of pralidoxime are scarce whereas the dosing scheme for obidoxime is clinically approved and safety data are available.

Therapy should be monitored by determination of the cholinesterase status: (1) acetylcholinesterase activity, (2) butyrylcholinesterase activity, (3) reactivatability of red blood cell acetylcholinesterase with an oxime, and (4) inhibitory activity of plasma towards test acetylcholinesterase. A ready-to-use kit for determination of these parameters is commercially available. This tool avoids therapeutic errors such as ending therapy prematurely, which might result in a restart of cholinergic crisis or unnecessary continuation of oxime application.

#### **4.7.3. Anticonvulsants**

Besides atropine, a central-acting anticonvulsant should be administered. Oximes poorly cross the blood-brain barrier. To protect the central nervous system from cholinergic excitation, diazepam should be given intravenously in 10-mg steps, repeated at 15-minute intervals until disappearance of convulsions, thus to minimise neurological sequelae. Doses of more than 40 mg might be necessary to stop overexcitation. In children each step should be 0.05-0.3 mg/kg. Alternatives are pentobarbitone, phenytoin, and lorazepam or sodium valproate. The possible use of levetiracetam and other antiepileptics is under investigation

#### **4.7.4. Overall clinical management**

In hospital, artificial ventilation, antidotal therapy, and general supportive treatment should be continued in function of symptomatology and overall clinical condition of the patient.

#### **4.7.5. Pretreatment**

In order to protect against the rapid aging of the enzyme-OP complex, particularly in soman and tabun poisoning, a pretreatment regime has been experimentally developed based on reversible carbamate cholinesterase inhibitors, for example, pyridostigmine three times per day. It does not prevent acute signs and symptoms, but enhances the

efficacy of antidotal treatment. At this time it is only available in some highly equipped and trained military forces and is not of relevance in a civilian context.

#### **4.8. Relevant clinical and toxicological investigations**

Besides symptomatology, measurement of decreased acetylcholinesterase and butyrylcholinesterase activity in blood are the only methods that are presently available to confirm the clinical diagnosis rapidly. A decrease of more than 20% of acetylcholinesterase activity in combination with mild symptoms indicates poisoning by a cholinesterase inhibitor (nerve agent or pesticide). Sensitivity can be increased via comparison to blank values previously established but these are usually available only for deployed personal.

Blood, urine, and tissue samples allow direct proof of presence of nerve agents and their metabolites or adducts in a patient. However, the analytical methods for these analyses are costly, laborious, and of little use for early clinical diagnosis. For forensic verification, however, samples should be taken in an appropriate way, thereby guaranteeing sampling and transport according to the regulations of “chain of custody”.

These laboratory approaches, which at the present state of development can only be performed in the laboratory, include (1) analysis of intact or hydrolysed nerve agent in blood and/or urine, (2) regeneration of nerve agent bound to proteins with fluoride ions and subsequent analysis of the phosphofluoridate, (3) detection of peptide adducts (products of a chemical reaction between an endogenous protein and the nerve agent) after proteolytic cleavage of a protein, for example, butyrylcholinesterase or serum albumin, and (4) hydrolysis of the phosphorylated protein and subsequent analysis of hydrolysed nerve agent and enzymatically formed metabolites thereof.

#### 4.9. Long-term health effects

OP-induced delayed neuropathy (OPIDN) is a symmetrical sensorimotor axonopathy, characterised by distal degeneration of some axons of both the peripheral and central nervous systems, and occurring 1 to 4 weeks after single or short-term exposures to certain organophosphorus agents. Cramping muscle pain in the lower limbs, distal numbness, and paraesthesiae occur, followed by progressive weakness, and depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. Signs include high-stepping gait associated with bilateral foot drop and, in severe cases, quadriplegia with foot and wrist drop as well as pyramidal signs. There is no specific treatment. Isometric tonifying exercises, stretching, prevention of Achilles tendon and other contractures, and gait and balance training should be done by physiotherapists. Ankle-foot orthosis may be indicated to overcome peripheral or central foot drop. Splints can be worn during the night to prevent flexion contractures. In time, there might be significant recovery of the peripheral nerve function but, depending on the degree of pyramidal involvement, spastic ataxia may be a permanent outcome.

OPIDN is due to the inhibition of a neuropathy target esterase. Nerve agents inhibit neuropathy target esterase but at much higher concentrations than needed for the inhibition of acetylcholinesterase. Even with optimal treatment, the probability that one should survive an acute nerve agent poisoning that is severe enough to produce OPIDN is, therefore, very low. After the Tokyo subway attack, a case of sensory axonopathy similar to OPIDN was described. The patient remained under intensive treatment and died 15 months after admission. At present, no such delayed effects have been reported among tabun or sarin survivors in Iran.

An “intermediate syndrome”, occurring between the acute episode and the OPIDN, has been described in organophosphorus insecticide poisoning in humans. It consists of marked weakness of proximal skeletal musculature and cranial nerve palsies, presenting 1 to 4 days after acute poisoning and requiring respiratory support. Prolonged



persistence of some OP insecticides in the body, prolonged cholinesterase inhibition, accumulation of acetylcholine at nicotinic synapses, and desensitisation of cholinergic receptors may all play a role. Antidotal treatment should be continued as described above. Respiratory support may become necessary, but it has not yet been described as a distinct clinical picture in nerve agent poisoning.

There is little doubt that severe poisoning by organophosphorus insecticides can cause behavioural and mental effects and long-term neuropsychological sequelae. In less severe poisonings the data are conflicting. Observations in Japan and Iran demonstrate that similar effects may occur after nerve agent OP poisoning, including a higher risk of lifetime posttraumatic stress disorder (PTSD), increased anxiety, increased depressive symptoms, fatigue, headache, and electroencephalographic (EEG) abnormalities. The most logical therapeutic implication would be to avoid, as much as possible, anoxia during the acute phase. The long-term follow-up of those patients requires the collaborative effort of neurologists, neuropsychologists, and psychiatrists.

#### **4.10. Outcome and prognosis**

Victims exposed unprotected to large doses of nerve agent and developing severe symptoms are unlikely to survive. After mild to moderate exposure and appropriate treatment, full recovery may take place. Antidotal treatment *per se* may, however, not be sufficient for survival. Assisted ventilation and general supportive measures will be required, sometimes for several days.

Repeated daily exposures are cumulative and may lead in the end to severe poisoning.

#### **4.11. Further reading**

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## Chapter 5:

# Lung-damaging (choking) agents

### 5.1. Introduction

Lung-damaging agents are chemical agents which produce a toxic inhalational injury as they attack lung tissue and primarily cause pulmonary oedema. Whether produced for military or industrial use, these CW agents pose a very real threat to military and civilian personnel alike (Figure 5.1).

The term choking agents has been traditionally applied to certain lung-damaging agents used as chemical weapons, and includes phosgene (CG), diphosgene (DP), chlorine (CL), and chloropicrin (PS). Several chemicals such as chlorine and phosgene are currently produced in large quantities for industrial purposes. Other toxic industrial chemicals which may cause toxic inhalational injury include ammonia, isocyanates, and mineral acids.

Smokes contain toxic compounds that cause the same effects as phosgene. Similar substances encountered in fires, for example, perfluoroisobutylene (PFIB), isocyanates, phosgene and hydrogen chloride (HCl), may also produce lung damage.

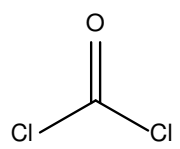
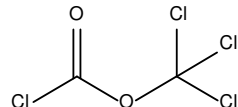

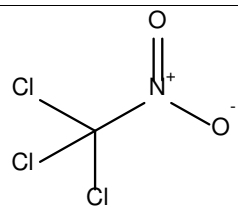


**Figure 5.1:** *The use of chlorine gas during World War I.*

## **5.2. Physical and chemical properties**

The physical and chemical properties of the more common lung-damaging agents are summarised in Table 5.1.

**Table 5.1:** Physical and chemical properties of the more common lung-damaging agents

Property	Phosgene (CG)	Diphosgene (DP)	Chlorine	Chloropicrin (PS)
Appearance	Colourless gas	Colourless liquid	Greenish-yellow gas, clear amber coloured liquid	Colourless liquid
Chemical formula	$\text{CCl}_2\text{O}$	$\text{C}_2\text{Cl}_4\text{O}_2$	$\text{Cl}_2$	$\text{CCl}_3\text{NO}_2$
Structure				
Molecular weight	98.92	197.83	70.9	164.39
Density ( $\text{g}/\text{cm}^3$ )	1.37 (20°C)	1.653 (20°C)		1.657 (20°C)
Freezing point (°C)	-127.8	-57	-100.98	-69.2
Boiling point (°C)	8.2	128	-34.05	112.2
Vapour density (0°C)	3.5	6.9	2.4	5.7
Vapour pressure (mm Hg) @ 20°C	1,173	4.2	5,031	18.3
Volatility ( $\text{mg}\cdot\text{m}^{-3}$ )	3,260,000 (0°C) 4,290,000 (7.6°C) 4,110,000 (20°C)	12,000 (0°C) 45,000 (20°C)		165,000 (20°C)

### **5.3. Detection**

Although field-detection equipment for classical choking agents is currently employed by some nations, and various commercial industrial detectors are available for a range of toxic industrial chemicals, there are no automatic detectors in service. The characteristic odour of some lung-damaging agents may be unreliable as a sure means of detection. For example, in low concentration, phosgene has a smell resembling newly mown hay, but the odour may be faint or lost after accommodation. There is also considerable variation in the sense of smell between individuals.

### **5.4. Protection**

The activated charcoal in the canister of chemical protective masks adsorbs phosgene, and in-service military respirators afford full protection from this and other choking agents.

### **5.5. Decontamination**

Clothes should be removed to prevent secondary contamination and further uptake. No other decontamination is required following exposure to classic choking agents or other lung-damaging agents in gas or vapour form.

### **5.6. Mechanism of action**

Chemicals that are highly reactive and/or highly soluble in aqueous solutions tend to act in the conducting, or central, compartment of the respiratory tract. Centrally acting irritants such as sulphur mustard, ammonia, and hydrochloric acid cause pronounced irritation of the epithelial cells lining the upper airway. Additionally, at low concentrations, centrally acting compounds are essentially consumed by deposition and reaction in the conducting airways before they reach the peripheral portion of the respiratory tract.

In contrast, most of the pulmonary agents, such as phosgene, oxides of nitrogen, and PFIB, are relatively insoluble and non-reactive, readily penetrating to the level of the respiratory bronchioles and the alveoli. There they undergo acylation reactions and are essentially consumed at that site, causing the damage that may eventually lead to pulmonary oedema.

After an asymptomatic or latent period of 20 minutes to 24 hours (depending on the exposure dose and physicochemical properties of the agent), fluid leakage into the pulmonary interstitium decreases compliance, producing a stiff lung and increasing complaint of tight chest, shortness of breath, and dyspnoea. Fluid eventually invades the alveoli and produces clinically evident pulmonary oedema.

## **5.7. Toxicity**

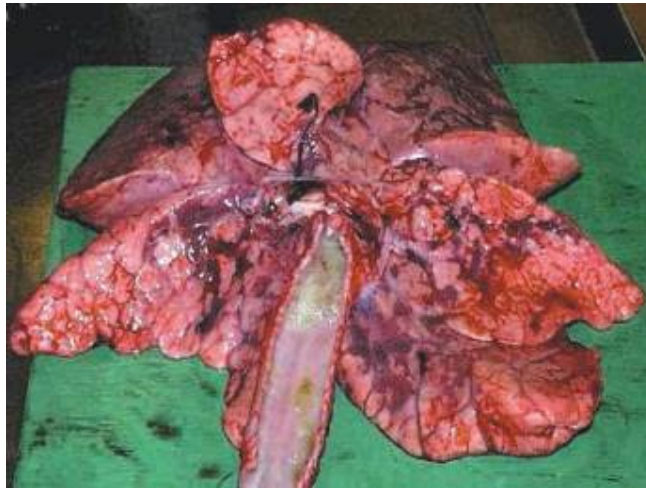
The odour threshold for phosgene is about  $1.5 \text{ mg}\cdot\text{m}^{-3}$ , and phosgene irritates mucous membranes at  $4 \text{ mg}\cdot\text{m}^{-3}$ . The LCt50 of phosgene is approximately  $3200 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ , which is half the LCt50 ( $6000 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ ) of chlorine, the first gas used on a large scale in World War I. Phosgene is twice as toxic as chlorine. Although it is less potent than almost all of the subsequently developed CW agents, this should not lead to an underestimation of its danger—deaths have occurred after the inhalation of only a few breaths of high concentrations of phosgene.

## **5.8. Signs and symptoms**

### **5.8.1. Pathology**

The outstanding feature of acute lung injury caused by lung-damaging agents is massive pulmonary oedema (Figure 5.2). This is preceded by damage to the bronchiolar epithelium, development of patchy areas of emphysema, partial atelectasis, and oedema of the perivascular connective tissue. Oedema fluid, usually frothy, pours from the bronchi and may be seen escaping from the mouth and nostrils. With exposure to very

high concentrations, death may occur within several hours; in most fatal cases pulmonary oedema reaches a maximum in 12 hours, followed by death in 24 to 48 hours. If the casualty survives, resolution commences within 48 hours and, in the absence of complicating infection, there may be little or no residual damage.



**Figure 5.2:** *Post-mortem appearance of the lungs following lethal exposure to phosgene. The lungs are hyperinflated due to the presence of pulmonary oedema and show focal parenchymal haemorrhage.*

### **5.8.2. Clinical effects**

Exposure to high concentrations of lung-damaging agent may irritate moist mucous membranes, depending on the agent's reactivity and solubility in water. A transient burning sensation in the eyes with lacrimation may coexist with early onset cough and a substernal ache with a sensation of pressure. Irritation of the larynx by very large concentrations of the agent may lead to sudden laryngeal spasm and death.

Pulmonary oedema follows a clinically latent period of variable length that depends primarily on the intensity of exposure but also partly on the physical activity of the exposed individual. This is particularly true for phosgene. After the latent period, the



patient experiences worsening respiratory distress that at first is unaccompanied by objectively verifiable signs of pulmonary damage, but may progress relentlessly to pulmonary oedema and death.

The most prominent symptom following the clinical latent period is dyspnoea, perceived as shortness of breath, with or without chest tightness, and in the initial stages there may be no objectively verifiable signs of pulmonary damage. The build-up of fluid in the lungs has two clinically pertinent effects:

- (1) Developing pulmonary oedema interferes with oxygen delivery to alveolar capillaries and may lead to hypoxemia. If a sufficient percentage of haemoglobin is non-oxygenated, cyanosis will become apparent.
- (2) The sequestration of plasma-derived fluid in the lungs (up to one litre per hour) may lead to hypovolemia and hypotension. Death results from respiratory failure, hypoxemia, hypovolemia, or a combination of these factors. Hypoxia and hypotension may progress particularly rapidly and suggest a poor prognosis.

The development of symptoms and signs of pulmonary oedema within four hours of exposure is an especially accurate indicator of a poor prognosis; in the absence of immediately available intensive medical support, such patients are at high risk of death. Complications include infection of damaged lungs and delayed deaths following such respiratory infections.

### **5.8.3. Differential diagnosis**

*Phosgene* is distinguished by its odour, its generalised mucous membrane irritation in high concentrations, dyspnoea, and pulmonary oedema of delayed onset.

*Riot-control agents* produce tearing, along with burning sensation and pain, predominantly in the eyes, upper airways, mucous membranes, and skin. This irritation is typically more intense than that caused by phosgene and is unaccompanied by the distinctive odour of phosgene.

*Nerve agents* induce the production of watery secretions as well as respiratory distress. However, their other characteristic effects (for example, muscle twitching and miosis) distinguish nerve agent toxicity from organohalide inhalation injury.

*Vesicants* usually produce a delayed respiratory toxicity associated predominantly with the central, rather than the peripheral, airways. Vesicant inhalation severe enough to cause dyspnoea typically causes signs of airway necrosis, often with pseudomembrane formation and partial or complete upper airway obstruction. Finally, pulmonary parenchymal damage following vesicant exposure usually manifests itself as haemorrhage rather than pulmonary oedema.

#### **5.8.4. Clinical investigations**

Sophisticated laboratory studies are of limited value in the immediate care of an exposed, injured individual. The following studies, however, are of some predictive value in determining the severity of exposure and the likely outcome.

##### *a) Chest radiograph*

The presence of hyperinflation suggests toxic injury of the smaller airways, which results in air being diffusely trapped in the alveoli. The presence of “batwing” infiltrates suggests pulmonary oedema secondary to toxic alveolar-capillary membrane damage. Atelectasis is often seen with more central toxic inhalant exposures. As radiological changes may lag behind clinical changes by hours to days, the chest radiograph may be of limited value, particularly if normal.

##### *B) Arterial blood gases*

Hypoxia often results from exposure to lung-damaging materials such as chlorine. Measurement of the partial pressure of oxygen ( $pO_2$ ) is a sensitive but non-specific tool in this setting; both the central and peripheral effects of pulmonary intoxicants may produce hypoxia. Arterial blood gases may show a low  $paO_2$  or  $paCO_2$ , which are early

nonspecific warnings of increased interstitial fluid in the lung. At 4 to 6 hours, normal arterial blood gas values are a strong indication that a particular exposure has little likelihood of producing a lethal effect.

*c) Pulmonary function tests*

Peak expiratory flow rate may decrease soon after a massive exposure. This non-specific test helps to assess the degree of airway damage and the effect of bronchodilator therapy. Decreased lung compliance and carbon dioxide diffusing capacity are particularly sensitive indicators of interstitial fluid volume in the lung, but are complex tests for hospital use only. Ventilation/perfusion ratio (V/Q) scanning is very sensitive but is nonspecific and for hospital use only.

## **5.9. Treatment of toxic inhalation injury**

### ***5.9.1. Medical Management***

*a) Termination of exposure*

Terminate exposure as a vital first measure. This may be accomplished by physically removing the casualty from the hazardous environment or by respiratory protection with a properly fitting respirator. Decontamination of liquid agent on clothing or skin terminates exposure from that source.

*b) Resuscitation*

Execute the ABCs of resuscitation (Airways, Breathing, Circulation) as required. Establishing an airway is especially crucial in a patient exhibiting hoarseness or stridor; such individuals may face impending laryngeal spasm and require intubation. Establishing a clear airway also aids in interpretation of auscultatory findings. Steps to minimise the work of breathing must be taken. Because of the danger of hypotension induced by pulmonary oedema or positive airway pressure, accurate determination of

the patient's circulatory status is vital, not just initially, but also at regularly repeated intervals and whenever indicated by the clinical situation. Carefully replace intravascular volume as required to maintain haemodynamic stability.

*c) Enforced rest*

Even minimal physical exertion may shorten the clinical latent period and increase the severity of respiratory symptoms and signs in an organohalide casualty. Physical activity in a symptomatic patient may precipitate acute clinical deterioration and even death. Strict limitation of activity (i.e. forced bed rest) and litter evacuation are mandatory for patients suspected of having inhaled any agent that might cause pulmonary oedema. This is true whether or not the patient has respiratory symptoms and whether or not objective evidence of pulmonary oedema is present.

*d) Prevention of lung oedema*

There is some clinical evidence that early administration of steroids may prevent development of toxic lung oedema when administration is started very early after exposure to relevant concentrations of toxic substances that are able to reach deep lung tissues, for example, in the case of phosgene exposure. Physicians should consider the early administration of such drugs whilst weighing up the known side effects of inhaled steroids.

*e) Airway secretions and bronchospasm*

Manage airway secretions and prevent or treat bronchospasm. Unless super-infection is present, secretions present in the airways of phosgene casualties are usually copious and watery. They may serve as an index of the degree of pulmonary oedema and do not require specific therapy apart from suction and drainage. Antibiotics should be reserved for those patients with an infectious process documented by sputum gram-staining and culture.

An elevation of the partial pressure of carbon dioxide ( $p\text{CO}_2$ ) greater than 45 mm Hg suggests that bronchospasm is the most likely cause of hypercapnia, and bronchodilators should therefore be used aggressively. Bronchospasm may occur in individuals with reactive airways, and these patients should receive beta-adrenergic bronchodilators.

Steroid therapy is also indicated for bronchospasm. Parenteral administration is the preferred route of steroid administration as inhaled routes may result in inadequate distribution to damaged airways. Methylprednisolone, 700 to 1000 mg, or its equivalent, may be given intravenously in divided doses during the first day and then tapered during the duration of the clinical illness. The increased susceptibility to bacterial infection during steroid therapy mandates careful surveillance of the patient.

*f) Treatment of pulmonary oedema*

Positive airway pressure (PAP) provides some control over the clinical complications of pulmonary oedema. Early use of a positive pressure mask may be beneficial, but PAP may exacerbate hypotension by decreasing thoracic venous return, necessitating intravenous fluid administration. Pulmonary oedema noted after a toxic inhalant exposure should be treated similarly to adult respiratory distress syndrome (ARDS) or “noncardiac” pulmonary oedema. The early application of positive end-expiratory pressure (PEEP) is desirable, possibly delaying or reducing the severity of pulmonary oedema. Diuretics are of limited value, but if they are used, it is useful to monitor their effect by measurement of the pulmonary artery wedge pressure, since excessive diuretics may predispose the patient to hypotension if PEEP or positive-pressure ventilation is applied.

### *g) Treatment of hypoxia*

Oxygen therapy is definitely indicated and may require supplemental PAP administered via one of several available devices for generating intermittent or continuous positive pressure. Intubation with or without ventilatory assistance may be required, and positive pressure may need to be applied during at least the end-expiratory phase of the ventilator cycle.

### *h) Treatment of hypotension*

Sequestration of plasma-derived fluid in the lungs may cause hypotension that may be exacerbated by positive airway pressure. Urgent intravenous administration of either crystalloid or colloid (which in this situation appear equally effective) should be commenced. The use of vasopressors is a temporary measure until fluids can be replaced.

## **5.9.2. Triage**

### *a) Within 12 hours of exposure*

A patient with pulmonary oedema is classified *immediate* only if intensive pulmonary care is immediately available. In general, a shorter latent period portends a more serious illness. A *delayed* patient is dyspnoeic without objective signs and should be observed closely and re-triaged hourly. An asymptomatic patient with known exposure should be classified *minimal* and observed and re-triaged every 2 hours. If the patient remains asymptomatic 24 hours after exposure, discharge the patient. If exposure is doubtful and the patient remains asymptomatic 12 hours following putative exposure, consider discharge. An *expectant* patient presents with pulmonary oedema, cyanosis, and hypotension. A casualty who presents with these signs within 4 hours after exposure is not expected to survive without immediate, intensive medical care including artificial ventilation.

b) *More than 12 hours after exposure*

A patient with pulmonary oedema is classified *immediate* provided he will receive intensive care within several hours. If cyanosis and hypotension are also present, triage the patient as *expectant*. A *delayed* patient is dyspnoeic and should be observed closely and re-triaged every 2 hours. If the patient is recovering, discharge 24 hours after exposure. A symptomatic patient or patient with resolving dyspnoea is classified *minimal*. If the patient is asymptomatic 24 hours after exposure, he is fit for discharge. A patient with persistent hypotension despite intensive medical care is *expectant*.

### 5.10. Further reading

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## **Chapter 6:**

### **Blood agents (cyanide compounds)**

#### **6.1. Physical and chemical properties**

Cyanide exists in several forms, including the gases hydrogen cyanide (HCN) and cyanogen chloride (CNCl), which are classified as blood agents due to the fact that they damage the oxygen-carrying capacity of red blood cells. Table 6.1 gives an overview of their most important properties.



**Table 6.1:** Properties of hydrogen cyanide and cyanogen chloride

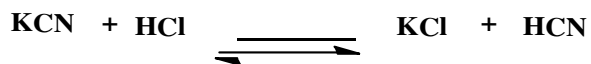
Properties	Hydrogen Cyanide	Cyanogen Chloride
Military Code	AC	CK
Melting point	-13.2°C	-6.9°C
Boiling point	27.7°C	13.0°C
Volatility (20°C)	837 mg·l <sup>-1</sup>	3,300 mg·l <sup>-1</sup>
Density	0.688 g·cm <sup>-3</sup>	1.186 g·cm <sup>-3</sup>
LC <sub>50</sub> (human) <sup>(a)</sup>	600 mg·min·m <sup>-3</sup>	11,000 mg·min·m <sup>-3</sup>
Solubility (H <sub>2</sub> O)	Freely soluble	Minor soluble
Odour	Bitter almond <sup>(b)</sup>	Strong odour <sup>(c)</sup>

<sup>(a)</sup> LC<sub>50</sub> is the vapour exposure that is lethal to 50% of the exposed population.

<sup>(b)</sup> Approximately 20 to 50% of the population does not easily detect the odour.

<sup>(c)</sup> Masking the bitter almond odour.

It should be noted that exposure to HCN can also result from the reaction with cyanide salts. When most inorganic cyanide salts come in contact with mineral acids (for example, sulphuric acid, hydrochloric acid), large quantities of HCN are formed as demonstrated with potassium cyanide (KCN):



Due to the acidity in the gastric milieu (pH ~1), significant concentrations of HCN could also be released when cyanide salts (for example, KCN) are ingested.

## **6.2. Toxicological properties and mechanism of toxicity**

### **6.2.1. Toxicokinetics**

HCN is extremely well absorbed by inhalation. Since HCN is non-ionised and of low molecular weight, significant absorption can occur at very high concentrations even through skin. Thereby, the dermal absorption rate is dependent on the pH of the cyanide solution. Lower pH values increase the dermal absorption rate because higher fractions of HCN exist.

Most cyanide salts are absorbed from mucous membranes within 1 minute after ingestion. When cyanide salts are placed in capsules, the absorption may be delayed for 20 to 40 minutes. Brief contact between small areas of skin and dry cyanide salts would not be expected to produce toxicity if the skin surface is intact. Injured skin (for example, abraded or burned skin) allows an accelerated absorption of cyanide salts.

At physiological pH (7.4), virtually all cyanide is present as HCN and distributes widely in the organism via blood circulation after absorption. Since cyanide reacts with high affinity with metals such as iron ( $\text{Fe}^{3+} > \text{Fe}^{2+}$ ) and cobalt, it binds reversibly to haemoglobin, especially methaemoglobin. Hence, cyanides are highly concentrated within red blood cells and this enhances the distribution of cyanides in the whole organism.

Under physiological conditions, HCN is detoxified by transulphuration, catalysed by a rhodanese enzyme system, to thiocyanate ( $\text{SCN}^-$ ), which is excreted in the urine. This metabolic pathway is particularly important for smokers because cigarette smoke commonly contains HCN (approximately 100 to 500  $\mu\text{g}$  per cigarette).

### **6.2.2. Toxicodynamics**

At toxic concentrations, cyanide inhibits many critical enzyme systems. This inhibition is most marked for cytochrome c oxidase, located in the mitochondrial inner membrane. Cytochrome c oxidase is the terminal enzyme in the electron transport chain and is responsible for oxygen consumption and energy generation. HCN binds mainly to the  $\text{Fe}^{3+}$  centre ion and inhibits the electron transport through this complex, thereby producing a decrease in oxidative phosphorylation and oxygen consumption. The resulting cellular hypoxia causes central nervous system and cardiovascular dysfunction. Additionally, cellular hypoxia forces an accelerated glycolytic conversion of glucose to lactate and an increased production of protons, caused by an imbalance between the rates of adenosine triphosphate (ATP) hydrolysis and synthesis. Therefore, serious cyanide poisoning is often accompanied by significant metabolic acidosis.

A lethal dose of HCN is estimated at 50 mg in an adult human. The lethal dose of KCN or NaCN (sodium salt of HCN) is estimated at 200 to 300 mg. It has been observed from accidents that 1 hour of continuous inhalational exposure of 100 ppm HCN was incompatible with life.

### **6.3. Clinical manifestations of exposure**

The symptoms of acute cyanide poisoning are nonspecific. However, a characteristic bitter almond smell of the exhalation air and ambient atmosphere can be detected. Using special analytical devices (for example, Dräger-Röhrchen®), sensitive and fast determination of the gaseous cyanide concentrations is possible ( $2 \text{ mg m}^{-3}$  within 2.5 seconds).

The main hallmarks are dysfunction of the central nervous system, cardiovascular toxicity, and metabolic acidosis. The development of toxicity is generally rapid. An exposure to high hydrogen cyanide concentrations can induce signs and symptoms immediately and result in death within minutes.

The most important and time-dependent symptoms of cyanide poisoning are shown in Table 6.2.

**Table 6.2:** *Time-dependent symptoms of cyanide poisoning*

<b>System</b>	<b>Early Signs</b>	<b>Later Signs</b>
Central nervous system	Headache, nausea and vomiting, anxiety, confusion, drowsiness	Altered consciousness, seizure, delirium, lethargy, convulsions, cerebral death
Cardiovascular system	Tachycardia, hypertension	Bradycardia, heart blocks, ventricular arrhythmias, cardiac arrest
Respiratory system	Dyspnoea, tachypnoea	Respiratory depression, non-cardiogenic pulmonary oedema,
<b>System</b>	<b>Early Signs</b>	<b>Later Signs</b>
		respiratory arrest
Blood	Bright red venous blood, pH < 7.35 (metabolic acidosis)	
Skin and eyes	Perspiration, bright red skin, cyanosis, mydriasis, eye irritation (following exposure to cyanogen chloride)	

The spectrum of symptoms is highly variable since the manifestation depends on the cyanide concentration and exposure time.

The toxicologic differential diagnosis of cyanide poisoning is difficult as asphyxiation (for example, inert gases, methane, nitrogen, carbon dioxide) and poisonings by other chemicals (for example, alcohols, sulphides, azide, arsine, methyl halides) exhibit similar

symptoms. Sudden unexpected collapse into unconsciousness or convulsions accompanied by metabolic acidosis and decreased oxygen consumption despite adequate oxygen delivery may be indicative of cyanide poisoning.

The absence of a significant delay between cyanide exposure and the onset of symptoms enhances the probability that cyanide poisoning will be recognised. The noting of an abnormal bitter almond odour may also be indicative of cyanide poisoning. As already mentioned, not all persons are able to detect the odour due to genetic variations.

#### **6.4. Triage (severity grading)**

In mass casualty situations in which cyanide poisoning is strongly suspected, the following triage criteria should be applied:

- Grade 1: No cyanide intoxication (patient is without any symptoms)
- Grade 2: Mild cyanide intoxication (patient is conscious)
- Grade 3: Severe cyanide intoxication (patient is unconscious)
- Grade 4: Lethal cyanide intoxication (patient is dead)

#### **6.5. Pre-hospital management**

##### **6.5.1. General aspects**

Cyanide is among the most rapidly acting and lethal of poisons, thus requiring immediate and aggressive treatment. The emergency diagnosis is uncertain because of the absence of characteristic signs and symptoms, and laboratory confirmation of cyanide intoxication takes hours to days. Nevertheless, treatment has to be started immediately without confirmed diagnosis.

When gaseous cyanides are released, health care personnel should wear appropriate protective equipment including butyl rubber gloves. It should be noted that a mask with a specially impregnated filter is required. The general management of acute cyanide poisoning entails the components outlined in Table 6.3.

**Table 6.3:** *General management of acute cyanide poisoning*

<b>Termination of exposure</b>	<ul style="list-style-type: none"> <li>– Inhalation exposure: removal from the scene of exposure (using appropriate personal protective equipment)</li> <li>– Ingestion exposure: gastric lavage, activated charcoal within 30 minutes</li> <li>– Dermal exposure: decontamination of skin with soap and water</li> </ul>
<b>Basic life support</b>	<ul style="list-style-type: none"> <li>– 100% oxygen (hyperbaric if possible)</li> <li>– Cardiopulmonary support or resuscitation</li> </ul>
<b>Advanced life support</b>	<ul style="list-style-type: none"> <li>– Sodium bicarbonate for metabolic acidosis</li> <li>– Anticonvulsants for seizures</li> <li>– Epinephrine for cardiovascular collapse</li> </ul>
<b>Antidotal treatment</b>	<ul style="list-style-type: none"> <li>– Methaemoglobin-forming agents (4-DMAP, amyl nitrite, or sodium nitrite), not recommended in smoke victims</li> <li>– Sodium thiosulphate</li> <li>– Hydroxycobalamin (smoke-inhalation victims)</li> </ul>

Even if a person has ingested lethal amounts of cyanide salts, the HCN concentration exhaled in the air is generally not high enough to cause major health problems for the emergency response staff. Nevertheless, mouth-to-mouth ventilation is not recommended.

Exposure to moderate to high cyanide concentrations can rapidly result in unconsciousness and lethal complications (respiratory arrest, cardiac arrest) within minutes. Therefore, antidotes have to be administered as soon as possible after cyanide exposure.

### 6.5.2. Medical treatment

Table 6.4 provides an overview of the doses and adverse effects of currently available antidotes:

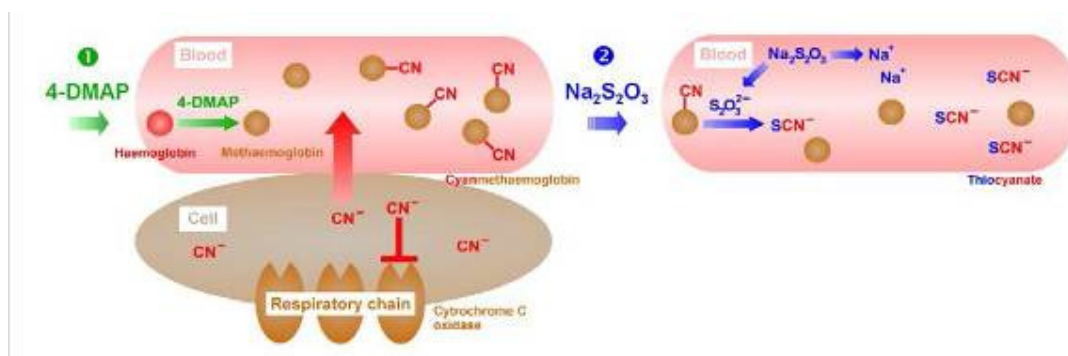
**Table 6.4:** Doses and adverse effects of currently available antidotes

Antidote	Dose	Mechanism	Adverse Effects
4-DMAP	3 – 4 mg·kg <sup>-1</sup> 5 ml (50 mg·ml <sup>-1</sup> ) intravenously (only one ampoule)	Methaemoglobin formation	Reduction of oxygen carrying capacity, overdose, haemolysis
Amyl nitrite pearls	1 pearl per minute via inhalation	Methaemoglobin formation	Reduction of oxygen carrying capacity
Sodium nitrite	4 mg·kg <sup>-1</sup> 10 ml (30 mg·ml <sup>-1</sup> ) intravenously	Methaemoglobin formation	Reduction of oxygen carrying capacity
Sodium thiosulphate	Ca. 100 mg·kg <sup>-1</sup> 30 ml (250 mg·ml <sup>-1</sup> ) intravenously	Enhancement of metabolism	Concentration >10 mg·dl <sup>-1</sup> : vomiting, psychosis, arthralgia, myalgia
Hydroxycobalamin	Initial: 5 g Additional: 10 g intravenously	Chelation of cyanide	Transient discoloration (skin, mucous membranes, urine), allergic reactions
Dicobalt edetate	4 mg·kg <sup>-1</sup> 20 ml (15 mg·ml <sup>-1</sup> ) intravenously	Chelation of cyanide	Severe hypotension, cardiac arrhythmias, convulsions

a) Methaemoglobin-forming agents

The antidotal mechanism of the methaemoglobin-forming 4-DMAP (4-dimethylaminophenol) and nitrites (amyl nitrite or sodium nitrite) is based on the higher affinity of cyanide for  $\text{Fe}^{3+}$ . Thus, 4-DMAP and nitrites oxidise haemoglobin ( $\text{Fe}^{2+}$ ) to methaemoglobin ( $\text{Fe}^{3+}$ ), which has a higher affinity for cyanide than haemoglobin. The preferential binding of cyanide to methaemoglobin, forming cyanmethaemoglobin, causes a rapid dissociation of cyanide from the cytochrome oxidase in the tissue, thereby reversing the inhibition of this enzyme. Additionally, 4-DMAP induces methaemoglobinaemia more rapidly than nitrite (30% methaemoglobin within 15 minutes, half-life of less than 1 minute). Amyl nitrite is absorbed rapidly via inhalation, and should be inhaled for 30 seconds out of each minute. The amyl nitrite pearls should be replaced with fresh ones every 2 to 4 minutes and should be broken in a gauze or cloth to avoid laceration injuries.

Co-administration of sodium thiosulphate with methaemoglobin-forming antidotes enhances the cyanide clearance. The combination of sodium thiosulphate and methaemoglobin-forming antidotes is very effective: an increase of tenfold in the lethal dose was observed in some animal studies. In the case of administering 4-DMAP, the same intravenous line can be used for the application of sodium thiosulphate (Figure 6.1).



**Figure 6.1:** Co-administration of the methaemoglobin-forming antidote 4-DMAP and the metabolism-enhancing antidote sodium thiosulphate accelerates the cyanide clearance.



It should be noted that methaemoglobin is not able to transport oxygen. Nevertheless, in healthy persons, methaemoglobin fractions of 20 to 30% are tolerated without life-threatening symptoms. The administration of a maximum of one ampoule (equivalent to  $3.3 \text{ mg kg}^{-1}$  4-DMAP in a 75-kg person) is recommended. In case of overdose, exceeded methaemoglobinaemia has to be corrected by  $2 \text{ mg}\cdot\text{kg}^{-1}$  of toluidine or  $1 \text{ mg}\cdot\text{kg}^{-1}$  of methylene blue to avoid haemolysis.

Methaemoglobinaemia is especially dangerous for smoke-inhalation victims, who often have concurrent carboxyhaemoglobinaemia due to exposure to carbon monoxide. Both methaemoglobinaemia and carboxyhaemoglobinaemia impair the oxygen transport capacity, and the administration of nitrites or 4-DMAP is not indicated.

#### *b) Metabolism-enhancing agents*

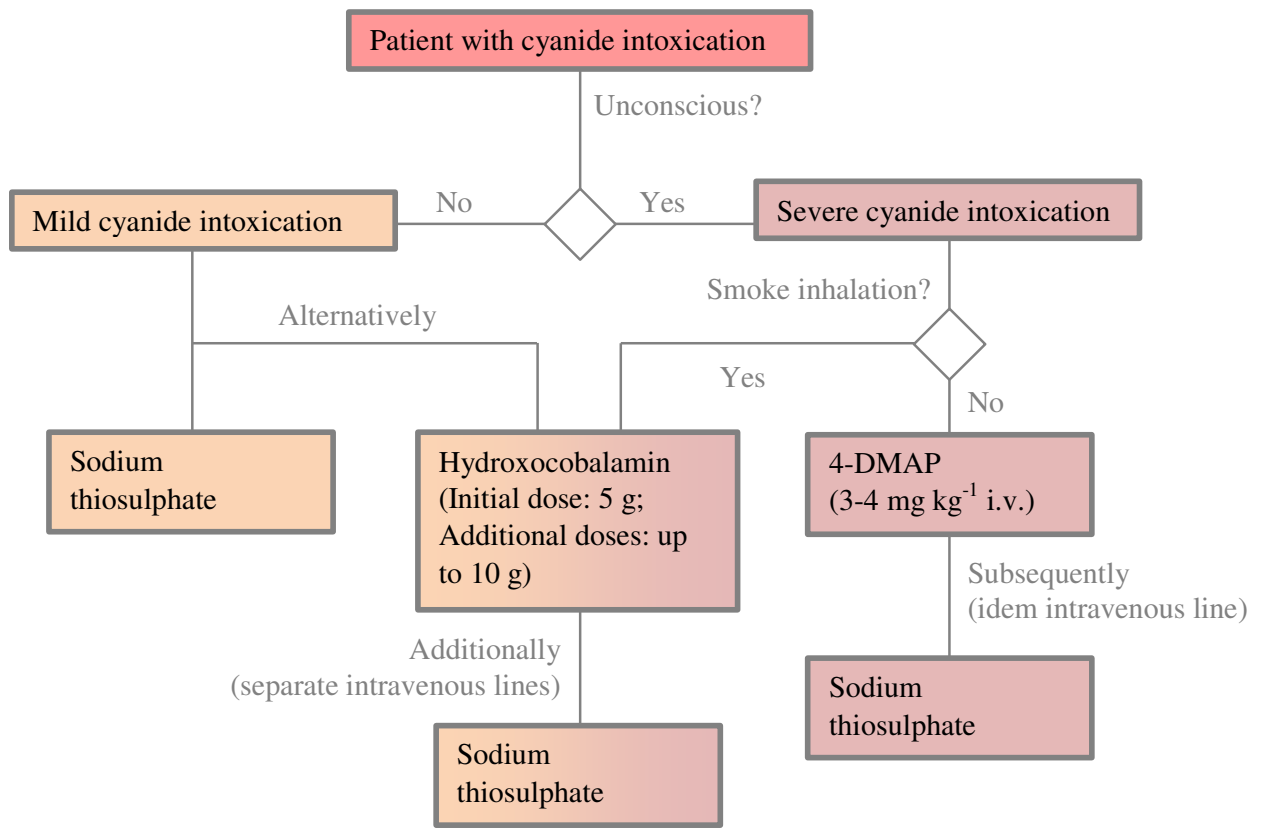
The intravenous administration of sodium thiosulphate accelerates the metabolism to thiocyanate, which is catalysed by the rhodanese enzyme complex. For enhancement of rhodanese enzymatic activity, thiosulphate increases the pool of sulphur equivalents by donating its sulphur group. The resulting thiocyanate is virtually non-toxic and is eliminated in the urine. Sodium thiosulphate suffers the disadvantage of limited distribution to the brain and limited penetration of the mitochondria in which enzymatic rhodanese is localised. The slow diffusion is responsible for delayed efficacy in cyanide poisoning. Thiosulphate is generally well tolerated, but it was shown in animal studies that in cases of significant overdose, the administration of sodium thiosulphate caused hypotension. As a precaution, sodium thiosulphate should be administered slowly over several minutes.

When the cyanide intoxication is mild, exclusive administration of sodium thiosulphate is generally sufficient.

### *c) Stoichiometric binding agents*

Cyanide-chelating agents (hydroxycobalamin or dicobalt edetate) are the first choice in treating patients with cyanide poisoning from smoke inhalation. Hydroxycobalamin or dicobalt edetate directly chelate cyanide from haemoglobin on an equimolar basis. In case of hydroxycobalamin, the reaction product cyanocobalamin is formed and then excreted in the urine. The safety risks are negligible and allow for infusion in cases without confirmation of cyanide poisoning. However, the administration is elongated in comparison to methaemoglobin-forming agents. First, solid hydroxycobalamin has to be reconstituted in saline before administration. Second, a high volume (100 ml) has to be infused. A further disadvantage is that hydroxycobalamin produces reddish-brown discoloration of skin, mucous membranes, urine, and plasma, which can interfere with some laboratory tests. Furthermore, its protection ratio is only 3 to 4. Practically, caution is required when administering a combination of hydroxycobalamin and thiosulphate since their combination may result in the formation of an inactive complex. Intravenous sodium thiosulphate should be given as a separate infusion after administering hydroxycobalamin.

The following flow chart (Figure 6-2) gives an overview how best to use the available cyanide antidotes:



**Figure 6.2:** Use of the available cyanide antidotes depends on type and severity of cyanide poisoning.

## 6.6. Hospital management

Some aspects of initial care in the emergency department are the same as those in the pre-hospital environment. These are described in Table 6.5.

**Table 6.5:** *Important aspects of the initial care in the emergency department*

<p><b>Initial care</b></p>	<ul style="list-style-type: none"> <li>– Decontamination (if not previously done)</li> <li>– Maintaining breathing and circulation</li> <li>– Antidotal treatment (if not previously administered)</li> <li>– 100% oxygen (if not previously administered)</li> <li>– Sodium bicarbonate (if not previously administered)</li> <li>– Admittance to the Intensive Care Unit</li> </ul>
<p><b>Intensive care unit</b></p>	<ul style="list-style-type: none"> <li>– Prosecution of oxygen, antidotes and sodium bicarbonate administering</li> <li>– Hyperbaric oxygen therapy (HBO) in smoke-inhalation victims, if applicable</li> <li>– Cardiac monitoring</li> <li>– Neurological monitoring</li> <li>– Treatment of coma, hypotension, seizures, and cardiac dysrhythmias in accordance with ACLS protocols (algorithms for advanced cardiac life support)</li> <li>– Monitoring for systemic toxicity of patients with chemical burns involving cyanides</li> </ul>
<p><b>Laboratory parameters</b></p>	<ul style="list-style-type: none"> <li>– Routine laboratory tests</li> <li>– Additional laboratory tests (plasma lactate, blood gas measurements)</li> <li>– Blood methaemoglobin concentration (should be &lt; 20%)</li> <li>– Blood carboxyhaemoglobin concentrations (additional in smoke-inhalation victims)</li> <li>– Blood cyanide concentrations (EDTA-blood): Standard value: 15 – 40 µg<sup>l</sup><sup>-1</sup> Toxic concentration: &gt; 200 µg<sup>l</sup><sup>-1</sup> Lethal concentration: &gt; 3 mg<sup>l</sup><sup>-1</sup></li> </ul>

Patients who have undergone serious skin contamination with cyanide salts should be decontaminated before transport to hospital since off-gassing of HCN may constitute a threat to the patient, rescuers and attendant medical personnel.

The patients should be observed closely for 24 hours in the hospital and regularly evaluated for evidence of cyanide poisoning.

If possible, total haemoglobin and methaemoglobin concentration should be measured rapidly before repeating a dose of methaemoglobin-forming antidotes. Blood cyanide concentrations should generally be interpreted with caution, as the short half-life of cyanide may lead to the underestimation of the cyanide values.

### **6.7. Long-term health effects**

After severe cyanide poisoning, in which hypoxic conditions occur for extended periods, long-term damage of the central nervous system is possible. Patients who survive severe cyanide intoxication may develop Parkinson-like symptoms with impaired motor function days to a month after exposure. These patients show abnormalities in the nigrostriatal dopaminergic system.

### **6.8. Treatment in long-term phase**

For treatment of the dopaminergic abnormalities that are similar to Parkinson's disease, dopamine agonists can be given but their efficacy and long-term tolerability have not been studied systematically.

### **6.9. Outcome and prognosis**

The prognosis of cyanide-poisoned patients depends on the form and dose of cyanide, the premorbid health status of the patient, the presence of other poisonings (for example, smoke inhalation), the pattern of injuries, and whether or not antidotes are administered.

## 6.10. Further reading

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# Chapter 7:

## Riot control agents

### 7.1. Introduction

Sensory irritants such as riot control agents are chemicals characterised by a very low toxicity, rapid onset, and a short duration of action. In general, these agents have a very wide margin of safety. 2-Chlorobenzalmalonitrile (CS) is the most commonly used sensory irritants for riot control purposes (Figure 7.1). 2-Chloracetophenone (CN) is also used in some countries for this purpose in spite of its higher toxicity. Dibenz(b,f)-1,4-oxazepine (CR) is a more modern irritant, but there is little experience of its use. The naturally occurring substance oleoresin capsicum (pepper spray), a mixture with capsaicin as the major pungent component, may find increased utilisation in law enforcement and riot control situations. Pepper spray is currently available over the counter for personal protection and in the US is used by postal carriers for repelling animals and by campers as a bear repellent.



**Figure 7.1:** *The use of the riot control agent CS during civilian unrest*

## 7.2. 2-Chlorobenzalmonitrile (CS)

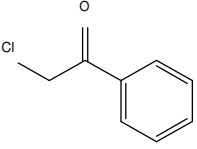
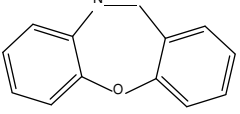
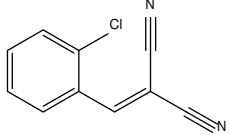
2-Chlorobenzalmonitrile (CS) is used as a riot control agent in many countries. It is also commonly used as a training agent for simulation of CW agent exposure and in the testing of respirator performance. The limit of the threshold of human detection (slight irritation of the nasal passages) of CS is approximately  $0.004 \text{ mg}\cdot\text{m}^{-3}$ . The minimal irritant concentration ranges from  $0.1$  to  $1.0 \text{ mg}\cdot\text{m}^{-3}$ , and intolerable signs and symptoms of exposure occur at concentrations of  $4.0$  to  $10.0 \text{ mg}\cdot\text{m}^{-3}$ . The estimated human lethal dose of CS is between  $25,000$  and  $150,000 \text{ mg}\cdot\text{min}\cdot\text{m}^{-3}$ , giving a safety ratio of the order of  $25,000$  to  $1,500,000$ .



### 7.2.1 Properties

The physicochemical properties of the riot control agents are summarised in Table 7.1.

**Table 7.1:** *Physicochemical properties of riot control agents*

Property	CN	CR	CS
Appearance	Colourless crystalline solid	Yellow needles	White crystalline solid
Chemical name	2-Chloroacetophenone	Dibenz[b,f]-1,4-oxazepine	2-Chlorobenzalmalonitrile
Chemical formula	C <sub>8</sub> H <sub>7</sub> ClO	C <sub>13</sub> H <sub>9</sub> NO	C <sub>10</sub> H <sub>5</sub> ClN <sub>2</sub>
Structure			
Molecular weight	154.59	195.29	188.6
Freezing point (°C)	57 – 58	71 – 72.5	95 – 96
Boiling point (°C)	244 – 245	335	310 – 315
Solubility in water	Practically insoluble	Slightly soluble	Practically insoluble
Solubility in organic solvents	Freely soluble	Freely soluble	Freely soluble
Vapour pressure (mm Hg) @20°C	0.013	0.000059	0.000034
Volatility (mg.m <sup>-3</sup> )	110 (20°C)	0.63 (25°C)	0.35 (20°C)

CS is usually dispersed as an aerosol generated pyrotechnically, but it can also be disseminated by spraying a solution of CS in a suitable solvent and as a very fine powder (micronised CS).

Although the smoke is non-persistent, CS may remain on rough surfaces (for example, clothes) from which it is released only slowly. At least 1 hour of aeration is necessary to cleanse such materials after exposure.

#### **7.2.2. Detection**

No field detectors for CS exist.

#### **7.2.3. Protection**

Full individual protective equipment will provide complete protection. Protection against field concentrations of CS is provided by the respirator and ordinary field clothing secured at the neck, wrists, and ankles.

#### **7.2.4. Decontamination**

Exposed persons should move to fresh air, separate from other contaminated individuals, face into the wind with eyes open and breathe deeply. Contaminated eyes and skin should be flushed with copious amounts of water. Following exposure, clothing and individual equipment should be inspected for residue. If a residue is found, individuals should change and wash their clothing to protect themselves and other unmasked persons.

#### **7.2.5. Mechanism of action**

Lachrymators act on nerve endings, the cornea, mucous membranes, and the skin. The reaction is very rapid.

#### **7.2.6. Signs and symptoms**

Exposure to CS causes the following symptoms:

- (1) *Eyes.* Symptoms include a violent burning sensation, conjunctivitis (lasting up to 30 minutes), erythema of the eyelids (lasting about an hour), blepharospasm,

violent lachrymation (over 10 to 15 minutes), and photophobia.

- (2) *Respiratory tract.* The first symptom is a burning sensation in the throat, developing into pain and extending to the trachea and bronchi. At a later stage, a sensation of suffocation may occur, often accompanied by fear. In addition, a burning sensation in the nose, rhinorrhoea, erythema of the nasal mucous membranes and sometimes mild epistaxis occur. The sense of taste is often distorted for some hours after exposure. Nausea, diarrhoea, and headache have been observed. Sneezing occurs after mild exposure and may be persistent. Many exposed people have reported fatigue for some hours afterwards. Coughing, choking, retching and (rarely) vomiting occur after exposure. Exposure to high concentrations of CS may result in pulmonary oedema.
- (3) *Skin.* A burning sensation occurs, especially in moist areas, but soon disappears. This burning sensation may recur some hours later, often while washing the area. Prolonged exposure to large amounts (for example, when handling CS in bulk) can cause erythema and vesicle formation. Prolonged exposure (continuous or intermittent) to high concentrations may result in a cumulative effect, particularly when combined with high temperatures and humidity. Sensitivity to CS may be provoked.

### **7.2.7. First aid**

In practically all cases it is sufficient to remove the casualty into fresh air; the symptoms will soon disappear. Clothing should be changed. If symptoms persist, the eyes, mouth and skin may be washed with water (and with soap in the case of the skin). Oil-based lotions should *not* be used. Skin decontaminants containing bleach should not be used but should be reserved for more dangerous contamination (for example, vesicants or nerve agents); bleach reacts with CS to form a combination which is more irritant to the skin than CS alone.

### **7.2.8. Treatment**

The salient points in the management of those exposed to CS are as follows:

- (1) *Eyes.* Ordinarily the eye effects are self-limiting and require no treatment. If large particles or droplets of agent have entered the eye, treatment for corrosive materials may be required. Prompt irrigation with copious amounts of water is the best treatment for solid CS in the eye. After complete decontamination, corticosteroid eye preparations may be used in consultation with an ophthalmologist.
- (2) *Skin.* Early erythema and stinging sensation (up to 1 hour), especially in warm moist skin areas, are usually transient and require no treatment. Inflammation and blistering similar to sunburn may occur after heavy or prolonged exposure, especially in fair skin. Corticosteroid cream or calamine lotion may be applied to treat existing dermatitis or to limit delayed erythema. If blisters develop, they should be treated as any other second degree burn. Secondary infection is treated with appropriate antibiotics.
- (3) *Respiratory tract.* In the rare event of pulmonary effects from massive exposure, evacuation is required. Management is the same as that for lung-damaging agents.

### **7.2.9. Course and prognosis**

Most personnel affected by riot control agents require no medical attention and casualties are rare.

### **7.3. Dibenz(b,f)-1,4-oxazepine (CR)**

Dibenz(b,f)-1,4-oxazepine (CR) is similar in its effects to CS, but the minimum effective concentration is lower and the LC<sub>t50</sub> is higher. Symptomatology and treatment are similar to those of CS.

CR differs from CS in being less toxic when inhaled but skin effects are more pronounced. It is, however, more persistent in the environment and on clothing.

#### **7.4. 2-Chloracetophenone (CN)**

2-Chloracetophenone (CN) is a riot control agent and as a training agent is now superseded by CS, the latter being much less toxic. However, it is still in use by police in some countries.

##### ***7.4.1. Properties***

CN is a clear yellowish brown solid which melts at around 54°C. Although poorly soluble in water, it freely dissolves in a wide range of organic solvents. When generated pyrotechnically, it is said to have a faint odour reminiscent of apple blossom.

##### ***7.4.2. Mode of action and toxic effects***

The mode of action is similar to that of CS; CN causes stimulation of sensory nerve endings.

##### ***7.4.3. Signs and symptoms***

Exposure to CN primarily affects the eyes, producing a burning sensation, lachrymation, inflammation and oedema of the eyelids, blepharospasm, and photophobia. After about 1 or 2 hours, all symptoms disappear.

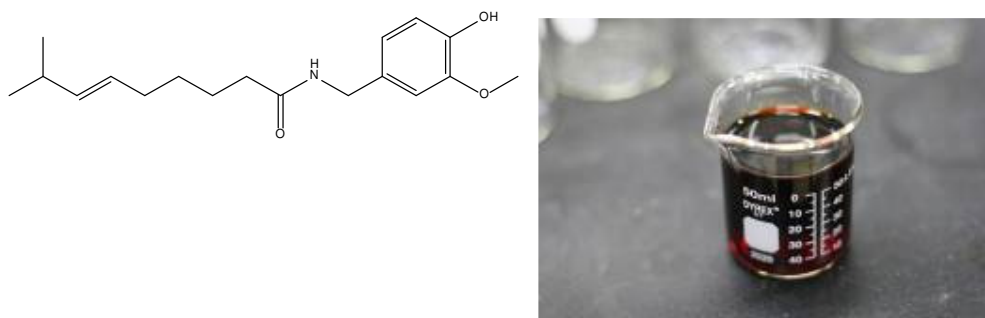
High concentrations can cause irritation of the upper respiratory tract, inflammation of the skin with blister formation, visual impairment, and pulmonary oedema. Drops or splashes in the eye may cause corrosive burns, corneal opacity, and even permanent visual impairment.

### 7.4.3. First aid

After exposure, ill effects are adequately neutralised by allowing fresh air to blow into the open eyes. If necessary, the eyes may be washed with copious amounts of water. The eyes should never be rubbed as mechanical injury may complicate the chemical effect. Patients suffering from temporary blindness should be reassured; permanent blindness from exposure to aerosol has never been observed, even at very high concentrations.

### 7.4. Capsaicin

Capsaicin is the most potent irritant component and quantitatively the major capsaicinoid of oleoresin capsicum (OC), an oily extract of plants of the genus *Capsicum* (peppers) (Figure 7.2). OC contains 0.01 to 1.0% of capsaicinoids on a dry mass basis. Commercially available pepper sprays contain 1 to 15% of capsaicinoids.



**Figure 7.2:** The chemical structure of capsaicin and the oily nature of oleoresin capsicum

Capsaicinoids activate the vanilloid receptors of sensory neurons. The release of the neuropeptide substance P, calcitonin gene-related peptide (CGRP), and neurokinin A produces alterations in the airway mucosa and neurogenic inflammation of the respiratory epithelium, airway blood vessels, glands, and smooth muscle.

Other capsaicinoids include nonivamide (pelargonic acid vanillylamide or PAVA). This capsaicinoid is present in low quantities in some *Capsicum* species, but it is synthesised for riot control purposes.

## 7.5. Further reading

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## Chapter 8:

# Toxic chemicals of biological origin

### 8.1. Introduction

Toxins are poisonous substances produced by biological organisms, including plants, animals, micro-organisms, viruses, fungi or infectious substances.

A wide range of substances are covered by the term 'toxin'. At one end of the range are the bacterial toxins, such as botulinum toxin and staphylococcal enterotoxin, both of which are high-molecular-weight proteins that have in the past been stockpiled for weapons purposes. In the middle of the range are the snake poisons, insect venoms, plant alkaloids and a host of other such substances, some of which, including ricin, have been used as weapons. At the other end of the range are relatively small molecules such as the marine toxins, some of which, including saxitoxin, have been weaponised. Hydrogen cyanide, which is covered in the Chapter 6 of this guidebook, is produced in commercial quantities by chemical synthesis, but is also a toxin as it occurs in some 400 varieties of plant, in certain animals, and is synthesized by at least one bacterium (*Bacillus pyocyaneus*).

This chapter discusses the medical effects and treatment of plant toxins and marine toxins, with a particular focus on ricin and saxitoxin, which are both listed in Schedule 1 of the CWC. Schedule 1 contains toxic chemicals which have been developed,



produced, stockpiled or used as chemical weapons, and are deemed to pose a high risk to the object and purpose of the CWC. Other chemicals listed on Schedule 1 include the blister agents and nerve agents which are discussed in Chapters 3 and 4 of this guidebook. Toxicological profiles of ricin and saxitoxin are summarized in Table 8.1.

**Table 8.1:** Brief toxicological profile of chemical weapons with toxinological origin

Chemical Agent	Biological Origin	Chemical Entity	Human Lethal Dose (µg/kg)	Routes of Entry	Onset of Symptoms After Exposure	Target System	Death After Exposure
Ricin	Castor beans	Glycoprotein	3	Inhalation, oral, injection	2 – 24 hours	GI* CV** NS*** RS****	36 – 72 hours
Saxitoxin	Shellfish	Non-protein guanidinium compound	5.7	Inhalation, oral, injection	0.5 – 2 hours	NS GI RS	2 – 12 hours

- \* GI = Gastrointestinal
- \*\* CV = Cardiovascular
- \*\*\* NS = Nervous system
- \*\*\*\* RS = Respiratory system

## 8.2. Ricin

Ricin is a toxic glycoprotein of the castor bean (*Ricinus communis L.*) that is strongly toxic to mammalian cells. The castor oil plant is a species of flowering plant in the spurge family, Euphorbiaceae. Pictures of the plant and castor beans are shown in Figure 8.1.



**Figure 8.1:** *Ricinus communis*, the castor oil plant, during flowering (left); castor bean formation (right); castor beans (below).

Ricin toxin is toxic when ingested, injected or even inhaled. Ricin is 1000-fold less toxic than botulinum toxin.

### **8.2.1. Historical use**

The US Department of War considered ricin as a potential weapon in 1918. It was code-named “compound W” by the US Army. American and British collaboration during World War II developed the W bomb, which was tested but never used. The first documented case of ricin poisoning as a weapon was the 1978 assassination of a Bulgarian defector, Georgi Markov. He was shot by a ricin-loaded platinum pellet from an umbrella in London. Ricin released from the pellet poisoned and killed Markov within three days. Six other terrorist attacks have been attributed to the same technique. The first prosecution under the U.S. 1989 Biological Weapons Anti-Terrorism Act was of two tax protesters convicted in 1995 of possessing ricin as a biological weapon in Brooten, Minnesota.

In 2003 in the US, a ricin-contaminated letter addressed to the White House was found in a mail room that served Senator Bill Frist in the Dirksen Senate Office Building. More recently, ricin-laced letters were sent to President Barack Obama and New York Mayor Michael Bloomberg, for which a Texas actress was convicted. Castor seed extracts have also been documented in suicide attempts. Five cases (four men and one woman) of attempted suicide by intravenous, intramuscular, or subcutaneous injection of self-made seed extract have been reported from Poland, Belgium, and the US. Many other cases of acute poisoning by ingestion of castor beans, as attempted suicide in adults and accident in children, have been reported that have had a low fatality rate.

### ***8.2.2. Physical, chemical and toxicological properties***

Ricin (64 kDa) is water soluble and thus is not found in castor oils. It consists of two peptide chains, A and B, which are linked by a disulphide bond. The B-subunit binds to glycoproteins in epithelial cells, enabling the A-subunit to enter the cell via receptor-mediated endocytosis. The A-subunit has the ability to modify catalytically the eukaryotic ribosomes, which blocks protein synthesis. One ricin molecule is able to deactivate 2,000 ribosomes per minute, which ultimately leads to the death of the cell. Ricin can also mediate apoptosis by mechanisms not yet fully understood. Other toxic effects include magnesium and calcium imbalance, cytokines release, acute phase reactions, and oxidative stress in the liver.

Ricin is most potent by inhalation and least toxic when used orally. The oral median lethal dose (LD<sub>50</sub>) in rodents is more than 1,000 times that by inhalation. The lower oral toxicity of ricin might be due its large size, which leads to gastric degradation and poor absorption in the gastrointestinal tract.

Ingested ricin is absorbed within 2 hours via blood and lymphatic vessels, accumulating in the liver and spleen. In experimental mice, ricin is detectable in faeces after 2 hours of oral gavage, but after 72 hours about 20 to 45% of ingested ricin is excreted unchanged via faeces. Ricin toxicity effects usually occur within 4 to 6 hours after ingestion but may

take as long as 10 hours.

Cytotoxic effects may occur up to 5 days after exposure, even in asymptomatic individuals. Most studies of oral ricin intoxication employed rodents, which have highly cornified layer of stratified epithelia on the luminal surfaces of their gastrointestinal tract, whereas the surface of the human gastrointestinal tract is minimally keratinised.

Macrophages of the reticuloendothelial system, such as Kupffer cells, have mannose receptors on the membrane surface, predisposing them to ricin toxicity. The resulting damage might persist for a long time and can progress to hepatic failure if a sufficient dose of ricin is ingested.

High doses of ricin injected intramuscularly or subcutaneously in humans cause local necrosis at the injection site, severe local lymphoid necrosis, liver necrosis, gastrointestinal haemorrhage, diffuse nephritis, and diffuse splenitis. The majority of the injected ricin is excreted through urine after 24 hours and less than 2% can be found in faeces.

### ***8.2.3. Clinical manifestations***

The majority of cases of oral ricin ingestion are related to the eating of castor beans, and more than 1,000 cases of toxic bean consumption have been reported, with a mortality rate of 1.9% to 6%. Release of ricin from castor beans requires digestion and delipidation of the bean matrix. Swallowed castor beans may pass intact through the gastrointestinal tract because of their solid shell-like coating.

The clinical manifestations of ricin poisoning occur within 2 to 24 hours, depending on the dose and route of entry, and death may ensue within 36 to 72 hours after exposure. The patients who ingested orally presented rapid onset of nausea, vomiting, and abdominal pain, followed by diarrhoea, haemorrhage from the anus, anuria, cramps, mydriasis, fever, thirst, sore throat, headache, vascular collapse, and shock. Oral ingestion of ricin may induce liver, spleen and kidney necrosis.

Intramuscular injection induces severe localised pain, and necrosis of regional lymph nodes and muscles, with moderate systemic signs such as fever, mydriasis, anuria, vascular collapse, and shock. Following inhalation, respiratory distress with pulmonary oedema occurs, which may lead to respiratory failure and death. Transient leucocytosis 2 to 5 times above normal may be observed.

Abdominal pain, oropharyngeal irritation, vomiting and diarrhoea are the primary clinical presentations of patients with castor bean intoxication. Different types of gastrointestinal bleeding such as haematemesis, melena, or haematochezia may occur because of local necrosis of the gastrointestinal tract. The volume loss causes dehydration, tachycardia, hypotension, and cyanosis. Hypovolemic shock and renal failure are induced by excessive volume loss. Hypoglycaemia and haemolysis are other common manifestations.

A sepsis-like syndrome including nausea, anorexia, headache, fever, hypotension and dizziness is an initial clinical presentation of intramuscular ricin injection, and may occur 10 to 12 hours post-injection. The injection site usually exhibits local tissue damage. Also present are increases in liver transaminases, creatinine kinase, amylase, and bilirubin, as well as renal insufficiency accompanied by myoglobinuria, lethal hypoglycaemia, and metabolic abnormality.

A 20-year-old man who committed suicide by injection of castor bean extract was admitted 36 hours post-injection. He presented with headache, abdominal, chest and back pain, nausea, severe weakness, and dizziness. He also had metabolic acidosis, anuria, and haematochezia. His manifestations progressed to low blood pressure, and renal and hepatic failure with bleeding diathesis, and did not respond to vasopressors and supportive care. Bleeding led to cardiac arrest, resistant to full resuscitative efforts. Haemorrhagic foci of pleura, brain, and myocardium were found on autopsy. The Bulgarian defector who was assassinated by injection immediately suffered from localised pain leading to general weakness over 5 hours. On admission, he had fever,

nausea, vomiting and tachycardia but normal blood pressure. On his thigh there was a 6-cm induration that was likely to have been the injection site. Regional lymph nodes of the affected limb were swollen. On the second day, he became tachycardic and hypotensive, and had leucocytosis ( $26,300/\text{mm}^3$ ). On the following day, he was anuric and had hematemesis and complete atrioventricular conduction block that led to death.

There is no report of fatal human ricin intoxication by aerosol but there have been reports of typical allergic syndrome including nose and throat congestion, itching eyes, urticaria, and chest tightness in workers exposed to castor bean dust. However, monkeys intoxicated with aerosolised ricin had no sign of systemic intoxication, but diffuse necrotising pneumonia, interstitial and alveolar inflammation, oedema, and alveolar flooding were observed.

The cause of death in ricin poisoning depends on the route of entry. However, as ricin is a relatively indiscriminate cellular toxin, all organs and systems are affected through systemic ricin intoxication. Oral ingestion of ricin induces necrotic and haemorrhagic lesions in the gastrointestinal tract, associated with hepatic and renal failure which leads to hypotension and vascular collapse not responding to treatment. Ricin injection also causes gastrointestinal haemorrhage, and hepatic and renal failure. Hypoxia secondary to pulmonary damage might be the main cause of death after ricin inhalation.

The main clinical manifestations of ricin and saxitoxin in different organs by routes of entry are summarised in Table 8.2.

**Table 8.2:** *Main clinical manifestations of ricin and saxitoxin*

Toxin	Oral Ingestion			Inhalation		Injection	
	Gastro-intestinal	Cardio-vascular	Nervous System	Respiratory	Nervous System	Nervous System	Cardio-vascular
Ricin	Nausea, vomiting, abdominal pain, diarrhoea, haematochezia, liver dysfunction, renal failure	Tachycardia, hypotension, shock, collapse	Fatigue, fever, muscle pain, weakness, dizziness	Cough, chest pain, dyspnoea, hypoxemia, non-cardiogenic pulmonary oedema	Fatigue, weakness, muscle pain, dizziness	Local pain, fatigue, dizziness	Tachycardia, hypotension, atrioventricular block
Saxitoxin	Nausea, vomiting	Tachycardia, hypotension, shock	Muscle pain, numbness and paralysis, dizziness, headache	Cough, chest pain, dyspnoea, respiratory failure	Muscle paralysis	Not reported in humans	

#### 8.2.4. Diagnosis

Ricin intoxication may explain pulmonary distress in a large number of healthy soldiers or even civilians as well as gastrointestinal haemorrhage in those who ingested the same food in a war or act of terrorism. Ricin injection should also be considered when a person at high risk for assassination or terrorism threat presents with rapid onset of one of the vascular leak syndromes such as oedema and hypotension.

Ricin is detected in tissue sections, body fluids, and nasal swabs by immunologically based methods like enzyme-linked immunosorbent assay (ELISA). Its lower limit of detection is around 0.1 ng/mL (1.54 pmol/L) and it can be detected up to 24 hours following exposure. Detection of ricin in environmental samples using time-resolved immunofluorescence assays and polymerase chain reaction (PCR) tests are also recommended. In a new method called immuno-PCR (IPCR), ricin is directly adsorbed onto wells of a microtitre plate or indirectly immobilised via a capture antibody. This method can detect amounts of ricin as low as 1 pg/mL with its limits of detection being 10 pg/ml in milk and egg samples, and 100 pg/ml in beef samples.

### **8.2.5. Triage**

Since the routes of exposure (IV, IM, inhalation, and oral) are different and the clinical manifestations of ricin intoxication may occur long after exposure, severity grading and triage is difficult in early stages. However, it should be done based on the history and clinical, toxicological and biochemical findings at certain times.

All exposed patients should be transferred to hospital and be examined by an emergency physician or ideally by a clinical toxicologist. Even asymptomatic patients must be under observation for at least 12 hours after ricin exposure. Patients with clinical manifestation and biochemical disturbances should ideally be treated in an intensive care unit (ICU).

### **8.2.6. Treatment**

There is no antidote for ricin poisoning and thus supportive care therapy is recommended. Ricin acts rapidly and irreversibly, therefore preventative measures such as vaccination of high risk groups, for example, military personnel or diplomatic persons at risk, are an important strategy consideration.

### **8.2.7. Decontamination**

On dermal exposure, remove all clothing and dressings, place the clothing in a durable 6-mm polyethylene bag and label them for discard as other CW agents. Wash the victim's skin with sufficient water and soap; alert patients should take a shower. After oral ingestion of ricin or castor beans, and in the absence of contraindications, gastric lavage and administration of activated charcoal should be performed. However, the adsorption rate of ricin by activated charcoal has not yet been quantitated and so its effectiveness has not been confirmed. On inhalational exposure, the patient must be removed from the decontaminated area immediately. It is recommended that surfaces and clothing be cleaned with a 0.1% sodium hypochlorite solution for at least 30 minutes.



Personnel who work in contaminated areas should protect themselves with personal protective equipment (PPE) such as a self-contained breathing apparatus (see Chapter 2). However, as at the first encounter the exact contaminating agents may not be known, it would be prudent to protect personnel using the highest protection level. Patients should be removed from the site of exposure and decontaminated in designated hazardous materials (HAZMAT) decontamination areas before being transferred to a hospital.

#### **8.2.8. Supportive care therapy**

Supportive care is the main treatment of ricin poisoning and differs depending on the route of ricin exposure. As cytotoxic effects of ricin may occur up to five days after intoxication, clinical and biochemical monitoring is recommended through this period, even in asymptomatic patients.

Intravenous or intramuscular ricin intoxication requires more careful monitoring for cardiovascular and lung functions. Prompt treatment of pulmonary oedema and hypotension is vital. Supportive therapy of acute pulmonary oedema and respiratory distress are indicated, such as administration of oxygen, anti-inflammatory agents, analgesics, artificial ventilation with positive-pressure breathing, and correction of fluids and electrolytes. Correction of coagulopathies and monitoring of liver and renal functions are also important.

Patients that remain asymptomatic up to 12 hours after exposure (oral or inhalational) are at low risk of developing toxicity and can be discharged but with some precautions. It should be remembered that cytotoxic effects of ricin may not occur for up to five days. Thus, biochemical monitoring is recommended throughout this 5-day period, even in asymptomatic patients. The ricin-intoxicated patients usually recover if they do not expire within 5 days after exposure.

The medicines difluoromethylornithine and dexamethasone have been recommended for treatment of ricin poisoning. They have induced longer survival times in intoxicated mice. During recent decades, researchers have tried to develop ricin inhibitors by reducing its N-glycosidase activity, but the more recent focus has been on molecules that disrupt intracellular trafficking. All these promising results are not yet ready for treatment in human cases.

Anti-ricin antibodies (anti-RTA, anti-RTB, and anti-ricin) were tested on preventing binding, internalisation or routing of RTA to the endosomal compartment, changing intracellular trafficking, and neutralising the ricin inside the cell. The results revealed that anti-RTA antibodies are more protective than anti-RTB antibodies based on in vitro studies. It is reported that some antibodies protect cells even 8 hours after cellular exposure. Other studies have demonstrated that animals can be protected against ricin by immunotherapy with monoclonal antibody (MAb). However, the majority of the developed MAbs against ricin have shown indifferent properties.

### ***8.2.9. Vaccination and passive protection***

Various high-risk groups need protection against ricin. Active vaccination is recommended for military personnel, very important or diplomatic individuals at high assassination risk, emergency first responders, and laboratory personnel investigating ricin. For civilians who are at low risk for exposure, a superior approach is post-exposure vaccination or antibody therapy. The general public should be vaccinated if there is a real risk of terrorist attack. Post-exposure vaccination needs rapid diagnosis and easy access to suitable vaccine.

The ideal ricin vaccine would protect victims against all routes of ricin intoxication and, for large emergency immunisations, should have a suitable half-life and provoke long-lived immunisation with only 1 or 2 doses. Different types of ricin toxoid, generated by heating or adding chemical substances, were evaluated in rodent models, administered subcutaneously or as aerosol. While reducing ricin-induced mortality, they failed to

protect against lung damage. Oral administration of ricin toxoids provides no protection against aerosolised ricin exposure. Another problem of the toxoid is residual risk of toxicity from inefficient inactivation. Inhalational exposure is best protected by active immunisation.

Another vaccine form is formalin-inactivated toxoid, although formalin cannot fully inactivate ricin. This type of vaccine is effective against aerosolised ricin. Recombinant ricin A chain vaccines have also been applied to reduce adverse effects of the vaccine and increase the stability. The US Army has developed RTA 1-33/44-198, a structurally modified ribosome-inactivating protein, which has afforded 100% protection of animals against supra-lethal doses of ricin aerosol.

A vaccine has been developed by a research group in Texas using a recombinant ricin A chain including the enzymatic and the vascular leak syndrome inducing sites. It is now known as RiVax™, and is highly soluble and stable in a variety of formulations. Intramuscular RiVax™ administration into mice protected lung functionality and tissue integrity against aerosol ricin in a dose-dependent manner. RiVax™ has already passed some clinical trials for safety and elicited ricin-neutralising antibodies in all volunteers at the high dose.

Inhalation of anti-ricin immunoglobulin (IgG) within the first hour of exposure could protect animals against lung lesions and reduce mortality rate. The anti-ricin immunoglobulin may also keep animals safe up to 2 to 3 days after administration, based on observed clearance rates of IgG from rabbits' airways. Applying anti-ricin IgG with a portable nebuliser immediately before an exposure is likely to provide some protection for non-immune individuals or reduce their toxicity manifestations.

### **8.3. Saxitoxin**

Saxitoxin (STX) is one of the most potent natural toxins known and is the best known paralytic shellfish toxin (PST). Saxitoxin has a large environmental and economic

impact, as its detection in shellfish such as mussels, clams, puffer fish, and scallops frequently leads to closures of commercial and recreational shellfish harvesting. Different types of creatures that may contain saxitoxin are shown in Figures 8.2 and 8.3.



**Figure 8.2:** *Different types of shellfish and crustaceans that might contain saxitoxin.*



**Figure 8.3:** *A puffer fish, which might contain saxitoxin.*

Saxitoxin was the first known and most studied toxic component of paralytic shellfish poisoning (PSP). The term saxitoxin originates from the species name of the butter clam, *Saxidomus giganteus*, in which it was first recognised. The term saxitoxin can also refer to the entire suite of related neurotoxins that are known collectively as saxitoxins.

They include saxitoxin (STX), neosaxitoxin (NSTX), gonyautoxin (GTX), and

decarbamoysaxitoxin (dcSTX). Ingestion of saxitoxin through shellfish contaminated by toxic algal blooms is responsible for PSP.

Saxitoxin causes muscular paralysis which may induce death or disable the person from performing any action or function. Saxitoxin can be delivered to victims via food, water, or air, and it can enter the body via open wounds. It may also be used in a penetrating device such as a syringe or other traumatising device like a dart that damages the skin and allows the toxin to enter the bloodstream. However, there have been no confirmed reports of homicidal poisoning by saxitoxin. The only reported suicidal saxitoxin poisoning is from Brazil, and was diagnosed during an epidemiological study for investigation of a saxitoxin-caused fatality in East Timor. The poisoning occurred as a result of eating a number of crabs containing this toxin.

### ***8.3.1. Toxicity***

The oral LD<sub>50</sub> of saxitoxin for humans is 5.7 µg/kg; therefore approximately 0.57 mg of saxitoxin is lethal if ingested and the lethal dose by injection is about ten times lower. The human inhalation toxicity of aerosolised saxitoxin is estimated to be 5 mg·min/m<sup>3</sup>. Saxitoxin induces high toxicity with a lethal dose of 50 µg/person.

Saxitoxin acts as a selective sodium channel blocker, preventing normal cellular function, and leading to paralysis.

### ***8.3.2. Clinical manifestations***

Exposure to saxitoxin commonly occurs following ingestion of certain fish that contain it in their tissues, but it may happen in chemical or biological warfare or in an act of terrorism. Ingestion of saxitoxin can cause numbness of the oral mucosa between 30 minutes and 2 hours after exposure. The numbness spreads to the face and neck in moderate cases and in severely intoxicated patients spreads to the extremities causing lack of coordination and breathing difficulty. Other reported symptoms may include nausea, dizziness, headache, anuria, and rapid onset of pain. After 12 hours, regardless

of severity, victims start gradually recovering and within a few days, with no residual symptoms.

In severe saxitoxin poisoning, illness typically progresses rapidly and may include gastrointestinal dysfunction (nausea, vomiting) and neurological manifestations, mainly cranial nerve dysfunction, a floating sensation, headache, muscle weakness, paraesthesia, and vertigo. Severe cases may also exhibit difficulty swallowing, incoherency or loss of speech. Respiratory failure and death can occur within 12 hours from muscle paralysis.

Clinical manifestations following inhalation may occur within 5 to 30 minutes, leading to paralysis and even death within 2 to 12 hours. Human cases of saxitoxin injection are very rare and have not been reported.

Saxitoxin poisoning can be confirmed even if toxicology testing is not performed because either a predominant amount of clinical and nonspecific laboratory evidence of a particular chemical is present or the aetiology of the agent is known with 100% certainty.

Cases involving circumoral paraesthesia, numbness or tingling of the face, arms and legs, ataxia, respiratory distress, headache, dizziness, weakness, nausea or vomiting within 15 minutes to 10 hours following the consumption of puffer fish are highly suggestive of saxitoxin intoxication.

The main clinical manifestations associated with ricin and saxitoxin by routes of entry in different organs were summarised in Table 8.2, as mentioned above.

#### ***8.3.4. Detection and diagnosis***

Detection of saxitoxin is a standard practice in the seafood industry. A variety of methods have been used ranging from bioassay to sophisticated chemical analyses. However, diagnosis of saxitoxin poisoning is based on history and clinical manifestations. Saxitoxin ingestion can begin to cause the effects in victims within 5 to

30 minutes. Clinical neurotoxicity and gastrointestinal dysfunction leading to muscle paralysis within 2 to 12 hours is highly suggestive of saxitoxin poisoning.

### **8.3.5. Triage**

Since the routes of exposure (IV, IM, inhalation and oral) are different and the clinical manifestations of saxitoxin intoxication may occur promptly, severity grading and triage is difficult in the early stages. However, it should be done based on history and clinical, toxicological, and biochemical findings at certain times.

All saxitoxin-exposed patients should immediately be transferred to hospital for examination by an emergency physician or ideally by a clinical toxicologist. If a large number of patients are exposed to saxitoxin, triage should be performed based on clinical findings and saxitoxin detection by an emergency or military physician or a clinical toxicologist.

### **8.3.6. Treatment**

A saxitoxin antitoxin is not practically effective, because the toxin acts so quickly in the nervous system. Therefore, supportive care therapy may allow the patient to survive the critical window of 12 hours from exposure. After oral saxitoxin ingestion, gastric aspiration and lavage must be done as soon as possible to prevent the toxin absorption. Activated charcoal is known to bind saxitoxin and thus should be administered after gastric lavage. Victims with severe saxitoxin poisoning will need artificial respiratory support, particularly those who were intoxicated by inhalation or by injection.

Several anti-saxitoxin antibodies revealed protection in experimental animals exposed to the toxin. However, these antibodies are quite specific and do not bind other saxitoxin analogues. Antitoxin must be given as soon as possible and once it is effective should be administered in sufficient amount to neutralise the toxin. This approach will provide a better chance of success in cases in which the onset and progression of toxicity is slow.

Alternative antibody-binding proteins which have potential as antitoxins are saxiphilins and a family of saxitoxin-binding proteins found in pufferfish. These groups of toxin-binding proteins are likely to remain stable in the bloodstream and could bind saxitoxin at nanomolar and even subnanomolar ranges. Thus, they may be as effective as the antitoxin that acts as a chelator.

One saxitoxin antidote may be created from a chemical that displaces saxitoxin from its binding site on its voltage-gated sodium channel. The drug 4-aminopyridine has been found in animal experiments to protect if not counteract saxitoxin, enhancing neuromuscular transmission to allow the diaphragm to function. Large doses of this drug are required, which may induce serious side effects in human cases and thus should only be used in a hospital to monitor and control the side effects. However, since saxitoxin toxicity occurs very fast, either the antitoxin or the medication will be effective if administered soon after exposure.

Supportive measures, particularly artificial respiration, may allow the patient to survive the critical lethality window of 12 hours.

#### **8.4. Further reading**

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[http://www.osha.gov/dts/osta/bestpractices/html/hospital\\_firstreceivers.htm](http://www.osha.gov/dts/osta/bestpractices/html/hospital_firstreceivers.htm)

or

<http://cdc.gov/niosh/unp-intrecppe.htm>

## Chapter 9:

# Summary and conclusions

### 9.1. Introduction and historical use of chemical weapons

The OPCW, the intergovernmental organisation established to implement and monitor the provisions of the Chemical Weapons Convention has been successful in overseeing the destruction of existing chemical weapons stockpiles, as well as leading efforts to prevent the re-emergence of chemical weapons, thus further reinforcing the historical taboo against the use of chemical weapons. So successful has been the OPCW that it was awarded the Nobel Peace Prize in 2013 (Figure 9.1). One of the outcomes has been motivation by the OPCW to increase its efforts to assist States Parties to be better prepared to deal medically with victims of exposure to these chemical weapons and to render them minimally effective or ineffective as tools of terror.



**Figure 9.1:** English certificate and medal of the Nobel Peace Prize for 2013

To accomplish this objective, the Technical Secretariat of the OPCW has compiled this guidebook containing a set of treatment guidelines to augment the clinical experience and training of physicians and other healthcare personnel. It is hoped that, taken together, the clinical experience and training of the health care personnel and the straightforward guidelines provided by this guidebook will provide the practitioner with a better understanding of the effects of exposure to chemical warfare (CW) agents and a clear confidence in the face of the influx of CW casualties. This understanding and confidence will translate into more effective treatment, a higher level of trust on the part of supporting medical personnel and patients, and, ultimately, less shock when faced with the use of CW agents.

Chapter 1 of this guidebook provides medical practitioners with an appreciation of the history of the development and use of chemical weapons, the types of chemicals which has been used as chemical weapons and a brief summary of the efforts of the international community to prohibit the use of chemical weapons.

## **9.2. Management of the chemical casualty situation**

Chapter 2 further provides information on CW agent detection and identification, and hazard avoidance, including definition and placement of “hot zones” and entry control, casualty decontamination, and general principles of triage. The chapter provides a reminder that management of a chemical incident aims to reduce or avoid secondary exposures, assure prompt assistance to victims, and achieve rapid and effective recovery. Chapter 2 renders the process of managing CW casualties an element of basic disaster management cycles. This assures maximum flexibility in terms of preventing “toxicological surprise” by diverse agents.

## **9.3. Blister agents**

Chapter 3 provides guidance for the acute and long-term management of blister agent casualties. Written and reviewed by physicians who have treated and monitored large

numbers of mustard casualties, mostly in armed conflict but also some from occupational exposure, this chapter provides invaluable information related to the pathophysiology of the mustard lesion and its acute management. The target organs for sulphur mustard are the eyes, the respiratory tract, and the skin, respectively, although not exclusively. The eyes are more susceptible to mustard than either the respiratory tract or the skin. Serious exposure irritates the eyes after 1 to 3 hours and produces severe lesions. Symptoms of respiratory tract involvement are cough, dyspnoea, and chest tightness, perhaps followed by laryngitis, tracheitis, and bronchitis. Skin injury follows a characteristic progression from erythema, oedema, and blistering. There is no specific drug therapy available for preventing the effects of mustard. Treatment is supportive and symptomatic, and aims to relieve symptoms, prevent infection, and promote healing. The chapter also describes the chronic health effects of mustard exposure and the rehabilitative and chronic care of mustard casualties. The long-term health effects of exposure to mustard agent may include prolonged psychological manifestations including PTSD, chronic depression, loss of libido and anxiety. Furthermore, long-term local effects of mustard exposure may include visual impairment, scarring of the skin, chronic obstructive airways disease, bronchial stenosis, gastrointestinal stenosis with dyspepsia, and increased sensitivity to mustard.

Finally, sulphur mustard is a known carcinogen. For example, American soldiers exposed to sulphur mustard during World War I experienced an increased incidence of lung cancer (and chronic bronchitis) compared to soldiers who had sustained other injuries. British workers involved in the production of sulphur mustard during World War II experienced an increase in the prevalence of laryngeal carcinoma (amongst those still alive).

The inclusion of the agent Lewisite in Chapter 3 is very relevant as it was weaponised in large quantities and mixed with sulphur mustard, because in addition to its toxic properties, it also depresses the freezing point of sulphur mustard, which was important in cold climates. In addition, according to UN inspectors in the Middle East, Lewisite

was also weaponised and stockpiled, albeit in small quantities relative to other munitions.

#### 9.4. Nerve agents

Chapter 4 provides a comprehensive description of the chemistry, pharmacology, and toxicology of, as well as countermeasures with regard to CW nerve agents. The chapter cautions that the classic CW nerve agents—tabun, sarin, soman, and VX—are examples of a broad class of compounds that act by phosphorylating the enzyme acetylcholinesterase (AChE), thus ultimately creating a profound CNS depression. This manifests as an early orthosympathetic crisis (the so-called “wet signs”: salivation, lacrimation, urination, and defecation), followed by a dominance of parasympathetic symptoms: bradycardia, hypertension, muscular twitching, fasciculations, weakness, and paralysis. Chapter 4 also describes prehospital and hospital management procedures, including patient decontamination and overall clinical management approaches. The OPCW has developed and implemented monitoring procedures to determine the presence of nerve agents in the environment, which may assist health care personnel in diagnostic evaluations (Figure 9.2).



**Figure 9.2:** *Under the guidance of the OPCW, inspectors monitor the environment of the Middle East for evidence of CW contamination.*

Chapter 4 also provides an important discussion of long-term health effects of exposures to nerve agents. The chapter includes discussions of the possibility of sensorimotor axonopathy, OP-induced delayed neuropathy (OPIDN), the unresolved question of an “intermediate syndrome” that is part of the acute phase of intoxication, and, finally, behavioural and mental effects and long-term neuropsychological sequelae.

### **9.5. Lung-damaging agents**

Chapter 5 provides an overview of the lung injuries resulting from chlorine, phosgene and other organohalides, oxides of nitrogen, and perfluoroisobutylene (PFIB), with emphasis on chlorine, the CW agent first used in modern warfare. Chlorine was suspected to have been used recently in Syria, and evidence has been collected regarding its deposition in the environment. Particularly useful is the treatment of differential diagnosis of other types of CW agent (blister, nerve and blood). The chapter’s main theme is the presentation of a roadmap for treatment of toxic inhalational injury:

- Triage,
- Treatment of exposure,
- ABCs of resuscitation,
- Enforced rest,
- Prevention of lung oedema,
- Management of airway secretions/prevention of bronchospasm,
- Treatment of pulmonary oedema, if it occurs, and
- Treatment of hypoxia and hypotension.

The rationale for these approaches is provided throughout the chapter, providing the reader with a clear picture of a general approach to treatment of toxicity and its rationale.

## 9.6. Blood agents

Chapter 6 discusses blood agents, so called because they impair the oxygen-carrying capacity of haemoglobin. At toxic concentrations the hallmarks of cyanide poisoning are the dysfunction of the central nervous system, cardiovascular toxicity, and metabolic acidosis. The development of toxicity is rapid, signs and symptoms appear quickly and death may result within minutes. The chapter provides a useful table providing early and later time-dependent manifestations of intoxication by cyanide.

Differential diagnosis of cyanide poisoning is difficult, as asphyxiation and poisoning by other chemicals produce similar symptoms. Again, the chapter provides useful guidance as to the differential diagnosis.

Table 6.4 in this chapter lists the currently available antidotes, their proposed mechanism of action, therapeutic dosages and potential adverse effects.

## 9.7. Riot control agents

Chapter 7 describes the health consequences of exposure to riot control agents. Non-lethal by design, the provisions of the CWC permit the use of riot control agents (sensory irritant chemicals) for law enforcement purposes (including domestic riot control), but prohibits the use of these chemicals as a method of warfare. Again, they are presented in this guidebook because of their use and potential health consequences in vulnerable populations, such as persons with reactive airways. Beginning with riot control agent CS (2-chlorobenzalmalonitrile), the chapter discusses signs and symptoms of exposure and prompt first aid approaches for riot control agents of like chemistry, namely, CR (dibenz(b,f)-1,4-oxazepine) and CN (2-chloroacetophenone), and capsaicin-based agents (pepper sprays).

## 9.8. Toxic chemicals of biological origin

Chapter 8 includes descriptions of the toxins ricin and saxitoxin, typical examples of marine and protein toxins, respectively, and which have diverse mechanisms of action and target organs. Extremely toxic, these agents require intensive supportive therapy, and international efforts are being made aiming to develop specific post-exposure vaccination or therapies for these exposures. Medical practitioners, particularly those involved in security and military departments, should be aware and advance their knowledge in diagnosis and clinical management of these highly toxic chemical/biological weapons.

Efforts to develop ricin as a toxin weapon for modern warfare grew partly from its wide availability in large quantities as a byproduct of the castor oil industry. In the second half of the 20th century the emergence of industrial-scale processing made for facile production. However, the military utility of ricin over other chemical weapons or even conventional weapons has remained questionable. Nonetheless this toxin has retained a mystique as a potential bioterrorism agent or assassination tool. It is currently monitored as a Schedule 1 toxic chemical under the CWC. The chapter provides valuable comments as to the requirements of supportive care in ricin poisoning.

Saxitoxin, on the other hand, targets specific sites in the nervous system, shutting down nerve transmission. The term saxitoxin refers to an entire suite of related neurotoxins that are known collectively as saxitoxins. They include saxitoxin (STX), neosaxitoxin (NSTX), gonyautoxin (GTX), and others. Ingestion of saxitoxin through shellfish contaminated by toxic algal blooms is responsible for the human illness known as paralytic shellfish poisoning (PSP). Exposure to saxitoxin most commonly occurs following ingestion of certain fish that contain it in their tissues, but exposure may happen in a chemical or biological war or an act of terrorism. Exposure initially induces a numbness around the mouth that spreads to the face and neck in moderate cases, and in severely intoxicated patients spreads to the extremities, causing lack of coordination



and breathing difficulty. As with ricin, supportive care is necessary and may allow the patient to survive the critical window of 12 hours from exposure. After oral saxitoxin ingestion, gastric aspiration and lavage must be done as soon as possible to prevent toxin absorption. Victims with severe saxitoxin poisoning will need artificial respiratory support, particularly those who were intoxicated by inhalation or by injection. The guidebook provides valuable cautions and directions for treatment and management of the toxin-exposed patient.

### **9.9. Concluding comments**

**The publication of this guidebook supports and promotes the provisions of the 1925 Geneva Protocol and the Chemical Weapons Convention by assisting in the development of a well-prepared medical response to support victims of exposure to chemical weapons, however that may occur.**

## **Annex 1:**

# **The Chemical Weapons Convention**

The negotiation of the Chemical Weapons Convention (CWC) that commenced in 1972 in Geneva was finally concluded in 1992. The CWC was recognised as being a revolution in arms control and disarmament. It was the first comprehensively verifiable multilateral treaty to completely ban an entire class of weapons, and firmly limit and monitor activities that may contribute to the production of those weapons.

The CWC goes further than any other treaty in terms of the scope of prohibition, and the depth, extent, and intrusiveness of verification provisions. Verification under the CWC includes compulsory national declarations about relevant industrial and military activities, and a regime of routine inspections of declared industrial and military facilities, including the stringent verification of destruction of all declared chemical weapons stockpiles. Additional features include the provision of a ‘challenge inspection’, under which a State Party can request at short notice an inspection of any site in another State Party, as well as provisions for the investigation of the alleged use of chemical weapons. These investigations of alleged use provisions were developed, to a large degree, based on experiences and lessons learnt in the conduct of the UN Secretary-General’s Mechanism, which was used several times during the Iran-Iraq war in the 1980s.

The treaty also provides for assistance to CWC States Parties (when under threat of attack by chemical weapons), and international cooperation to facilitate the development of chemistry for peaceful purposes. In addition, the treaty required the establishment of a new international organisation to administer the treaty, the Organisation for the Prohibition of Chemical Weapons (OPCW), including an inspectorate to undertake the various verification tasks.

The ‘general purpose’ definition of chemical weapons in the CWC effectively means that any toxic chemical that is being used as for chemical warfare (CW) purposes is a chemical weapon. This broad definition was necessary because there are many dual-use chemicals used for legitimate peaceful purposes that can also be used in the development of chemical weapons (for example, chlorine). Also, it was important to ensure that all new toxic chemicals discovered or developed in the future (for example, chemicals acting on the central nervous system and ‘mid-spectrum’ agents) would also be captured by the CWC prohibition of chemical warfare.

In addition to the broad definition of chemical weapons, the CWC Verification Annex lists three schedules of chemicals deemed to pose a particular level of risk to the objective of the Convention. For example, Schedule 1 includes blister agents, nerve agents (and their binary precursors) and two toxins (ricin and saxitoxin). Schedule 2 contains other toxic chemicals (including the nerve agent amiton and the psychochemical BZ) and key precursors to a range of CW agents. Schedule 3 contains some of the other CW agents used in World War I (including phosgene and hydrogen cyanide) as well as other precursors (including earlier precursors for nerve agents). The lists of chemicals contained in the schedules form the basis of the mandatory declarations and routine industry inspections under the CWC.

The UN Secretary-General’s Mechanism was used in 2013 to investigate reports of large-scale use of chemical weapons in Syria. The UN investigation mechanism was used rather than an OPCW investigation of alleged use because Syria was not a State Party at

the time of attack. Several OPCW inspectors were members of the inspection team requested by the UN Secretary-General to investigate the alleged use of chemical weapons.

In May 2014, the OPCW did conduct an investigation of alleged use in Syria, confirming that chlorine (a choking agent) had been used. The OPCW has provided chemical security guidelines to States Parties to reduce the possibility that dual-purpose chemicals such as chlorine (used commercially for water purification) could be obtained and used for hostile purposes.

In addition to the CWC, the efforts of the international community to strengthen the prohibitions against chemical weapons have resulted in a number of additional international activities and agreements designed to strengthen the prohibition of use of chemical weapons. These range from actions taken by the UN (including General Assembly and Security Council resolutions, such as resolution 1540), to the development of national export licensing measures and chemical security measures on toxic industrial chemicals (including classes of pharmaceuticals) that could be used for chemical warfare purposes.

The Chemical Weapons Convention, supported by these various complementary international and national measures, has been largely recognised as a success story and is generally regarded as having greatly reduced the possibility of large-scale use of chemical weapons as a method of warfare.

#### **ANX1.1. Further reading**

Official website of the Organisation for the Prohibition of Chemical Weapons:

[www.opcw.org](http://www.opcw.org)

## **Annex 2:**

### **Classes of chemical warfare agents**

#### **ANX2.1. Blister agents**

Blister agents, or vesicants, are amongst the most common chemical warfare (CW) agents. These oily substances act via inhalation and contact with skin. They affect the eyes, respiratory tract, and skin, first as an irritant and then as a cell poison. As the name suggests, blister agents cause large and often life-threatening skin blisters which resemble severe burns. Examples include sulphur mustard (H, HD), the nitrogen mustards (HN1, HN2, and HN3), Lewisite (L), and phosgene oxime (CX).

Sulphur mustard and Lewisite are the blister agents that have been most widely weaponised and used in combat operations. These agents produce casualties in the battlefield and force opposing troops to wear full protective equipment, thus slowing the tempo of military operations.

Sulphur mustard was first used by Germany in 1917, and has been used in several conflicts since, notably in the Iran-Iraq War (1980 to 1988). Sulphur mustard was used extensively in the Iran-Iraq war, resulting in more than 100,000 casualties, with more than 30,000 of these casualties subsequently dying from the long-term effects. Apparently more than 70,000 of the Iranian survivors of sulphur mustard exposure are still under constant medical treatment.

Lewisite was weaponised in large quantity (sometimes mixed with sulphur mustard) and was used by Japan in World War II. These two agents are primarily dispersed in liquid or vapour (aerosol) form and are regarded as persistent agents, as the toxic hazard may persist for many days.

Nitrogen mustard (HN-3) was weaponised during World War II but was apparently not used in combat operations. There does not appear have been either large-scale weaponisation or use of phosgene oxime.

### **ANX2.2. Nerve agents**

In the 1930s, German companies were undertaking research into improving insecticides and discovered very toxic organophosphorus compounds. The military authorities were informed and this led to the development of nerve agents tabun and then sarin. Tabun was produced for the first time in December 1936 and was being manufactured and weaponised by 1939. During WWII, Germany produced several thousand tonnes of tabun and smaller amounts of sarin.

In the early 1950s, industrial research in the UK attempting to develop more effective pesticides led to the discovery of the nerve agent amiton, which was used for a short time in agriculture, but was then withdrawn because of its high mammalian toxicity. Following research in military establishments, it was subsequently discovered that replacing one of the phosphorus-alkoxy bonds in amiton (subsequently code-named VG) with a phosphorus-methyl bond increased by the toxicity by at least a factor of 10. This led to the development and weaponisation of the V-series of nerve agents, with the development and weaponisation of VX by the US, and the development and weaponisation of homologues of VX (including Vx by the former Soviet Union. In the 1980s, Iraq was considering the production and weaponisation of amiton. Not surprisingly, the physical and toxicological properties of VX and Vx are similar, and methods of medical treatment of the V-series agents are also very similar.

Nerve agents acquired their name because they affect the transmission of nerve impulses in the nervous system. They are stable and easily dispersed, extremely toxic and have rapid effects both when absorbed through the skin and via respiration. Poisoning may also occur through consumption of liquids or foods contaminated with nerve agents. It is interesting to note that organophosphorus insecticides currently in use have a similar structure to the organophosphorus nerve agents and, although they have a similar effect on the human body, they are less toxic.

The volatility of nerve agents varies widely. For example, the consistency of VX may be likened to a relatively involatile oil, and it is therefore a persistent CW agent. Its effect is mainly through direct contact with the skin, although it presents a serious inhalation hazard as an aerosol and, in warmer weather, as a vapour that can be inhaled. Sarin, on the other hand, is a liquid with volatility comparable to water, and is mainly taken up through the respiratory organs. The volatilities of soman, tabun, and GF (cyclohexylsarin) are between those of sarin and VX. Thickeners can be added to volatile CW agents, including soman, which increases their persistence.

### **ANX2.3. Choking agents**

Choking agents were among the first CW agents produced in large quantities and were first used by Germany near Ieper on 22 April 1915. Both sides used choking agents extensively during WWI. Initially the CW agents were released from gas cylinders, and were subsequently released from artillery shells and mortars. Examples of choking agents include chlorine (CL), phosgene (CG), diphosgene (DP) and chloropicrin (PS). These choking agents were found useful in WWI, particularly in trench-warfare situations, because these CW agents are heavier than air, and therefore would fill the trenches.

#### **ANX2.4. Blood agents**

The name blood agent, like those of other groups of agents, derives from its effect on victims. Blood agents are distributed via the blood and generally enter the body via inhalation. They inhibit the ability of blood cells to utilise and transfer oxygen. Thus, blood agents are poisons that effectively cause the body to suffocate. The main two blood agents used in chemical warfare are hydrogen cyanide (AC) and cyanogen chloride (CK).

Hydrogen cyanide (sometimes mixed with metal chlorides) was used to a limited extent in World War I, and was found to have very limited military advantage (for example, compared with phosgene) because hydrogen cyanide is lighter than air which made it difficult to generate significant concentrations on the battlefield. Cyanogen chloride was also used to a limited extent in World War I, but it was also not considered as effective as phosgene.

However, the concentration of hydrogen cyanide may rapidly reach lethal levels and lead to rapid death if it is released in confined spaces. For example, during World War II, a form of hydrogen cyanide (zyklon B) was used in the Nazi gas chambers. Hydrogen cyanide was weaponised in World War II by Japan (including in glass hand grenades), but was apparently not used extensively.

#### **ANX2.5. Sensory irritants (riot control agents)**

Sensory irritants are chemicals that are capable, when used in field concentrations, of rapidly causing temporary disablement that lasts for little longer than the period of exposure. Their harassing effects, which arise from the reflex responses of the body to sensory irritation, include lachrymation, sternutation, vomiting and pain. They have been widely used as riot control agents and also in armed conflict.

Sensory irritants were the first type of CW agent used during World War I. A range of sensory irritants were considered for use in World War I, including xylol bromide, ethyl



bromoacetate and a number of other halogenated organic chemicals, and oleoresin capsicum (OC), the natural oil of chili peppers. During World War II, several thousands of tonnes of sensory irritants were stockpiled, mainly 2-chloroacetophenone (CN), a lachrymator, and adamsite (DM), a sternutator. With some of these sensory irritants, the safety ratio was low enough that some serious casualties or deaths could occur.

In 1959, 2-chlorobenzalmalonitrile (CS) was developed as a riot control agent. This chemical affects the mucous membranes at very low concentrations and causes stinging, tearing, and general discomfort. However, it has an extremely high safety ratio, making it almost impossible to create a dangerous dose outdoors. For this reason, CS rapidly became the preferred sensory irritant for use both in law enforcement including domestic riot control, as well as in military operations.

The issue of sensory irritants was the topic of long and heated debates during the CWC negotiations, where they were generally referred to as riot control agents (RCAs). At issue was their inclusion in the treaty and the restrictions that would be imposed upon their use. In the end, a compromise was reached under which States Parties are required to declare to the OPCW the RCAs they possess for law enforcement purposes. Though use is allowed for these purposes, it is prohibited to use RCAs as a method of warfare.

#### **ANX2.6. Marine toxins**

Many toxins are produced by marine organisms. One such example is saxitoxin (STX), which is synthesised by a type of blue-green algae (cyanobacteria). These algae provide food for different shellfish, for example, mussels. The mussels themselves are not influenced by the poison, but human beings who later eat the mussels may become seriously ill.

Saxitoxin attacks the nervous system and has a paralysing effect, but causes no symptoms in the gastrointestinal tract. The development of the illness is extremely rapid, and at high doses death may occur within less than 15 minutes. The LD<sub>50</sub> value

for humans is at about 1 mg. Saxitoxin is a relatively small molecule with a molecular weight of 370 D. It is not sensitive to heat but is destroyed by oxygen. Saxitoxin is included in Schedule 1 of the CWC.

#### **ANX2.7. Plant toxins**

The seeds of the castor oil plant can be used to extract ricin, a mixture of poisonous proteins. One of these has also been produced by *Escherichia coli* bacteria to which the ricin gene has been transferred.

Ricin became of interest as a CW agent at an early stage as it is relatively easy to produce in large quantities. In 1978, it was used in the “umbrella murder” in London where a ricin-treated bullet was used to shoot a Bulgarian defector, who died within three days. Ricin is included in Schedule 1 of the CWC.

## **Annex 3:**

### **Other toxic chemicals that could be used as chemical warfare agents**

The chemical warfare (CW) agents considered in Chapters 3 to 8 of this guidebook are not the only toxic chemicals that can kill or injure on a large scale.

In the last century, many thousands of toxic chemicals have been investigated for their potential utility as military weapons. However, relatively few have been found capable of meeting military requirements of an effective CW agent (including effectiveness in military operations, capability of being readily produced in militarily significant quantities, and stability in storage), and fewer still have been made into weapons and actually been used. However, the deliberate releases of toxic chemicals against which public health authorities would need to prepare might include attacks by non-State entities whose agent-selection principles could differ from those used by the military. For example, accessibility, rather than overall aggressiveness and stability in storage, might be the dominant criterion in their choice of toxic chemical.

With the success of the Chemical Weapons Convention (CWC) in destroying existing stockpiles of chemical weapons and in preventing the re-emergence of new stockpiles, other albeit less toxic chemicals might be used nowadays. This may be especially true where accessibility or terrorising potential rather than casualty cost-effectiveness

dominates weapons choice.

There are many commercial chemicals that could cause great harm, exemplified by the large numbers of casualties caused by the accidental release of methyl isocyanate in Bhopal, India, in 1984. Commercial chemicals of this type are often referred to as toxic industrial chemicals (TICs).

Therefore, medical practitioners who may be called upon to treat patients suspected of being exposed to CW agents should be aware that there are other toxic chemicals that could be used for chemical warfare purposes, and they should have ready access to information on the toxic properties and treatment of these types of chemicals. Some of these chemicals are briefly discussed below.

### **ANX3.1. Toxic industrial chemicals**

Some high-hazard TICs, as identified by a NATO International Task Force in 2001, are shown in Table A4.1 below. This list includes chlorine, hydrogen cyanide and phosgene, which have already been used as CW agents and which are discussed in this guidebook. Hydrogen cyanide and phosgene are listed in Schedule 3 of the CWC.

**Table A4.1:** *Examples of high-hazard toxic industrial chemicals*

Ammonia	Arsine	Boron trichloride
Boron trifluoride	Carbon disulphide	Chlorine
Diborane	Ethylene oxide	Fluorine
Formaldehyde	Hydrogen bromide	Hydrogen chloride
Hydrogen cyanide	Hydrogen fluoride	Hydrogen sulphide
Fuming nitric acid	Phosgene	Phosphorus trichloride
Sulphur dioxide	Sulphuric acid	Tungsten hexafluoride

When medical practitioners are considering which toxic chemical(s) their patient may have been exposed to, it is therefore appropriate to take into account not only the CW agents covered in Chapters 3 to 8 of this guidebook, but also other TICs which may be diverted from their intended peaceful application and used as CW agents in either armed conflict or for chemical terrorism purposes.

### **ANX3.2. Other toxic chemicals, including pharmaceutical-based chemicals**

In addition to TICs, a number of other toxic chemicals not covered in Chapters 3 to 8 of this guidebook, have the potential to be used as CW agents, either in armed conflict, or for chemical terrorism purposes. Such toxic chemicals include perfluoroisobutene (PFIB), central nervous system acting agents including BZ and opioids, and bioregulators.

#### ***ANX3.2.1. Perfluoroisobutene***

Also known as 1,1,3,3,3-pentafluoro-2-(trifluoromethyl)-1-propene, perfluoroisobutene (PFIB) is a rapid-acting lung irritant that damages the air-blood barrier of the lungs and causes oedema. It is a colourless, odourless gas at most ambient temperatures and is easily liquefied. PFIB 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. Inhalation is the principal route of exposure. High concentrations may produce irritation of the eyes, nose, and throat. A syndrome known as “polymer fume fever” has been described following inhalation of PFIB.

PFIB is listed in Schedule 2A of the CWC. More details on PFIB, including information on latency period and recovery time, main clinical symptoms, principles of medical management and prophylaxis/therapy are provided in *Public health response to biological and chemical weapons: WHO guidance* (2004), pages 156 to 160.

### **ANX3.2.2. Toxic chemicals that act on the central nervous system**

Following World War II, the US and the former Soviet Union were both actively developing CW agents that targeted the central nervous system (CNS). The chemicals considered included substances which, when administered in low doses, cause conditions similar to psychotic disorders or other symptoms emanating from the central nervous system (such as loss of feeling, paralysis, or rigidity). During the 1950s, studies were made of substances including glycolic acid esters (glycolates), phencyclidine, and LSD. Particular interest was paid to the glycolic acid ester 3-quinuclidinylbenzilate (BZ), which in low concentrations causes peripheral symptoms such as distended pupils, deteriorated short-distance vision, dry mouth, and palpitations, and in higher concentrations causes increased body temperature, deterioration in the level of consciousness, hallucinations, and coma. Incapacitating after-effects were found to persist up to 1 to 3 weeks after the exposure.

During the 1960s, psychochemical warfare agents including BZ and its homologues were weaponised. These chemicals were traditionally commonly referred to as incapacitating chemical agents (ICAs). However, the effects of these toxic chemicals were found to be difficult to predict and there was uncertainty about the effectiveness of these CW agents on the battlefield. As a consequence, both countries chose to destroy their stockpiles of psychochemical agents in the 1980s. More details on BZ, including information on latency period and recovery time, main clinical symptoms, principles of medical management and prophylaxis/therapy are provided in World Health Organization Manual (2004), pp.186-190. BZ is listed in Schedule 2A of the CWC.

The Scientific Advisory Board (SAB) of the OPCW has recently expressed concerns that opioids, including fentanyl (used as an anaesthetic in surgical procedures) and its homologues (including carfentanyl, which is used in darts to subdue large animals) could be used for hostile purposes prohibited by the CWC. For example, fentanyl homologues are powerful synthetic opiate analgesics similar to, but more potent than,

morphine, and some have LD<sub>50</sub> values comparable to VX nerve agent. These chemicals are also sometimes referred to ICAs, however, the term may not be appropriate for these types of chemicals, because it is not possible to control the release of a vapourised or aerosolised CNS-acting chemical in such a way so that each exposed individual receives a safe ‘incapacitating’ dose.

### **ANX3.2.3. Bioregulators**

During recent years, concerns have been expressed about the risk of bioregulators being used as CW agents. They are closely related to substances normally found in the body and may be algogenic (causing pain), anaesthetic, or influencing blood pressure. A characteristic of them is that they are active in extremely low doses and frequently have rapid effect.

### **ANX3.3. Further reading**

World Health Organization. *Public health response to biological and chemical weapons: WHO guidance*. Geneva: WHO Press; 2004.

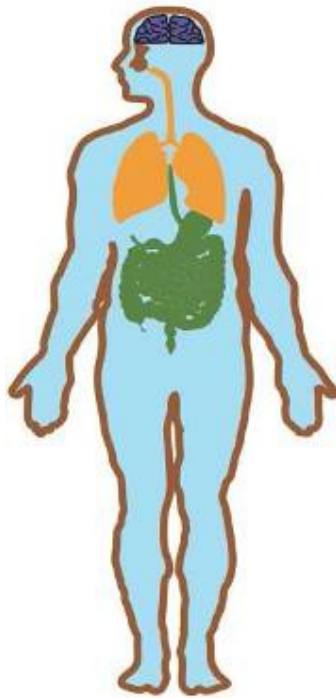
NATO International Task Force 25 (ITF-25). *Reconnaissance of industrial hazards*. Quoted in: World Health Organization. *Public health response to biological and chemical weapons: WHO guidance*. Geneva: WHO Press; 2004.

*Patty's Toxicology 6<sup>th</sup> Ed.* Eula Bingham and Barbara Cohrsenn, editors. (Wiley 2012)

Scientific Advisory Board of the OPCW. *Report of the Scientific Advisory Board on developments in science and technology for the Third Review Conference; RC-3/WP.1*, dated 27 March 2013. The Hague: Organisation for the Prohibition of Chemical Weapons; 2013.

**Annex 4:**  
**Symptoms and signs of exposure to different  
classes of CW agents**





TARGET ORGANS	CLASSES OF AGENT
<p><b>CENTRAL NERVOUS SYSTEM</b></p> <p>Seizures, coma, hypoxemia</p> <p>Hyperthermia</p>	<p>Blood /Nerve / Blister / BZ</p> <p>BZ</p>
<p><b>EYE, NOSE AND SKIN</b></p> <p>Constricted pupils</p> <p>Dilated pupils</p> <p>Dry mouth and skin</p> <p>Eye irritation</p> <p>Blistering of skin</p> <p>Cyanosis</p>	<p>Nerve</p> <p>Nerve / Blood</p> <p>BZ</p> <p>Blister / RCAs / Lung irritants</p> <p>Blister</p> <p>Blood/ Lung / Nerve / Blister</p>
<p><b>RESPIRATORY TRACT</b></p> <p>Asphyxiation</p> <p>Copious secretions</p> <p>Respiratory distress</p> <p>Pulmonary oedema</p>	<p>Blood / Lung / Blister / Nerve</p> <p>Nerve</p> <p>Nerve / Lung / Blister</p> <p>Lung / Nerve / Blister</p>
<p><b>DIGESTIVE TRACT</b></p> <p>Nausea</p> <p>Diarrhoea</p>	<p>Lung / RCAs / Blood / Nerve</p> <p>Nerve</p>
<p><b>MUSCOSKELETAL</b></p> <p>Fasciculation</p>	<p>Nerve</p>

#### **ANX4.1. Explanatory notes:**

The clinical symptoms and signs shown in the above diagram are intended to provide preliminary guidance to the type of CW agent that a casualty may have possibly been exposed to, based on the major symptoms that would be expected to be caused by the different classes of CW agents.

It should be noted, however, that additional symptoms and signs to those indicated in the diagram may sometimes be exhibited following exposure to other CW agents. For example, exposure to very high concentrations of sulphur mustard may also cause CNS-effects.

In addition to the major clinical features listed above for each class of CW agent, there may also be other serious effects. For example, exposure to the blood agent cyanogen chloride (CK) causes eye irritation as well as cyanosis.

Respiratory signs and symptoms may be present following exposure to any of the CW agent discussed in Chapters 3 to 8, as well as many of the other toxic chemicals listed in Annex 3.

It should be recognised that individual patients may present differently. Therefore, the overall pattern of clinical signs presented by a range of patients should be considered.

The full list of symptoms and signs provided in Chapters 3 to 8 should be consulted for further information to assist the medical practitioner in making a clinical diagnosis.

Additional information is available in the WHO Interim Guidance Document, *Initial clinical management of patients exposed to chemical weapons* (2014).

## **Annex 5:**

### **Long-term consequences of exposure to chemical warfare agents**

The most prominent short-term effect of exposure to CW agents is the large number of casualties that they can cause. 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 chemical weapon attack may be more serious than that caused by an attack with conventional weapons.

The possible long-term consequences of the exposure to CW agents, including chronic illness and delayed effects, are more uncertain and less well understood than the acute effects following exposure to CW agents.

*Chronic illness* after exposure to some CW agents is well known. The occurrence of chronic debilitating pulmonary disease in victims of exposure to sulphur mustard was reported after the World War I. This has also been described in reports on the current status of Iranian casualties from Iraqi use of mustard gas during the war between Iraq and Iran in the 1980s. Follow-up of Iranian victims has revealed debilitating long-term disease of the lungs (chronic bronchitis, bronchiectasis, asthmatic bronchitis, chronic obstructive pulmonary disease, pulmonary fibrosis, and large airway obstructions), eyes (delayed sulphur mustard keratitis with dryness and loss of vision), and skin (dry and

itchy skin, with multiple secondary complications, pigmentation disorders, and structural abnormalities ranging from hypertrophy to atrophy). Deaths from pulmonary complications are still occurring many years after all exposure ended. A more detailed discussion of the long-term effects of exposure to sulphur mustard is contained in Chapter 3.

*Delayed effects* in persons exposed to certain chemical agents, depending on the dose received, may include carcinogenesis, teratogenesis, and perhaps mutagenesis. For example, some chemicals of particular concern, such as sulphur mustard, are alkylating agents, and many such agents have been found to be carcinogenic. In addition to their ability to cause physical injury and illness, CW agents may lend themselves to psychological warfare (which is a military term for attacks on morale, including terrorisation) because of the horror and dread that they can inspire.

However, it is recognised that there are often great difficulties associated with assessing the long-term health effects of exposure to CW agents. For example, even with sulphur mustard, in which there is a clear link between exposure and long-term health effects, there may be confounding variables which may make it difficult to draw a definitive conclusion for a particular patient. In particular, it may be difficult to distinguish genuine long-term effects of exposure to CW agents from background occurrence of the same symptoms due to a wide spectrum of other causes such as lifestyle influences, for example, smoking, and environmental exposure to other chemicals and sunlight. In situations where there is conflicting data and inconclusive results, it will be even more difficult to reach a definitive conclusion for each patient as to whether their current health status is linked to previous exposure to CW agents.

But despite the difficulties associated with assessing the long-term health effects of exposure to CW agents, and because of the severity of the long-term health effects, a medical response programme should make provision not only for the immediate casualty-producing potential of such agents, but also for possible long-term consequences.

## List of Abbreviation and Glossary

**AC:** The military symbol for hydrogen cyanide. *See Blood agents.*

**Acetylcholine:** The neurotransmitter substance at cholinergic synapses that causes cardiac inhibition, vasodilation, gastrointestinal peristalsis and other parasympathetic effects.

**AchE:** Acetylcholinesterase is the enzyme that catalyses the breakdown of acetylcholine and of some other choline esters that function as neurotransmitters.

**Aerosol:** A finely atomised solid or liquid, in the form of small droplets, which behaves in the same way as a cloud of gas when dispersed.

**Antidote:** A medicine for counteracting / neutralizing the harmful effects of a poison.

**APR:** Air –purifying respirator.

**ARDS:** Adult respiratory distress syndrome.

**ATP:** Adenosine triphosphate.

**BAL:** British anti-Lewisite. A dimercaprol ointment applied to skin which has been exposed to Lewisite to relieve the blistering.

**Blister agents:** Blister agents are toxic chemicals that cause severe skin, eye and mucosal pain and irritation leading to skin blisters, for example, sulphur mustard, Lewisite, nitrogen mustards and phosgene oxime. Also known as vesicants.

**Blood agents:** The common name given to the class of CW agents that interfere with oxygen utilisation at the cellular level, and include hydrogen cyanide (AC) and cyanogen chloride (CK).

**BZ:** 3-Quinuclidinyl benzilate. *See incapacitating agents.*

**CG:** Phosgene. *See lung damaging agents..*

**Choking agents:** *See lung damaging agents.*

**CI:** Chemical incident: The release (either intentional or unintentional) of one or more hazardous chemicals which could harm human health or the environment.

**CK:** Cyanogen chloride. *See Blood agents*

**CN:** 2-Chloroacetophenone (CN) is used in some countries for riot control purposes in spite of its higher toxicity than CS. *See Riot Control Agents.*

**CS:** 2-Chlorobenzalmalonitrile is the most commonly used sensory irritant for riot control purposes. *See Riot Control Agents.*

**CR:** Dibenz(b,f)-1,4-oxazepine. *See Riot Control Agents.*

**CW:** Chemical warfare is the use of toxic chemicals that can cause death or injury through their chemical action, as a means or method of warfare.

**CW agent:** A chemical warfare agent is a toxic chemical that can cause death or injury through its chemical action, which has been developed, produced or stockpiled as a chemical weapon, or which poses a risk to the object and purpose of the CWC by virtue of its potential for use in activities prohibited by the CWC.

**Chemical weapon:** A chemical weapon consists of a toxic chemical (CW agent) that can cause death or injury through its chemical action, contained in a delivery system such as a bomb, rocket or artillery shell. The Chemical Weapons Convention defines chemical

weapons more broadly to include precursors to CW agents, and all CW agent delivery systems, including improvised means of delivery.

**CWC:** The Chemical Weapons Convention. The full title is: Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction. The CWC was opened for signature 13 January 1993, entered into force 29 April 1997.

**CX:** Phosgene oxime. *See Blister agents.*

**Cytotoxic:** Being toxic to cells which may result in cell death.

**Decontamination:** The rendering harmless of a dangerous substance (for example, CW agents) by removing, destroying, or covering it.

**Detection:** Demonstrating the presence of a particular CW agent and/or measuring its concentration.

**4-DMAP:** 4-Dimethylaminophenol.

**DMPS:** Dimercaptopropanesulphonic acid.

**DMSA:** Dimercaptosuccinic acid.

**DP:** Diphosgene. *See lung damaging agents.*

**EPA:** Environmental Protection Agency.

**Exposure:** Being subjected to radiation or chemicals with potentially harmful effects.

**GA:** Military code for the nerve agent tabun. *See Nerve agents.*

**GB:** Military code for the nerve agent sarin. *See Nerve agents.*

**GD:** Military code for the nerve agent soman. *See Nerve agents.*



**GF:** Military code for the nerve agent cyclohexyl sarin. *See Nerve agents.*

**GTX:** Gonyautoxin - *see STX Saxitoxin.*

**HAZMAT:** Hazardous materials.

**HCN:** Hydrogen cyanide. *See Blood agents.*

**H:** Military code for sulphur mustard. A vesicant chemical warfare agent which is highly reactive and forms blisters on the exposed skin as well as the respiratory and eyes complications. HD is the military code for distilled sulphur mustard.

**HD:** *See H.*

**HN:** Military code for the nitrogen mustards. A family of mustard compounds with the central atom of nitrogen, which are used as chemotherapeutic medicines. HN1, HN2 and HN3 are the military codes for the three nitrogen mustards. HN3 was weaponised during World War II.

**HN1, HN2, HN3:** *See HN.*

**IC:** Incident commander.

**ICA:** Incapacitating chemical agent. A chemical designed to put an enemy completely out of action for several hours or days, but with a disablement from which full recovery is possible without medical assistance. BZ, a central nervous system depressant that blocks the muscarinic action of acetylcholine, was weaponised for this purpose.

**ICS:** Incident command system. The ICS is a system that coordinates all resources needed in the management of a chemical incident through a unified incident commander (IC).

**IPCR:** Immuno-Polymerase Chain Reaction.

**L:** Military code for Lewisite. *See Blister agents.*

**Lung damaging agents:** A class of toxic chemicals which produce a toxic inhalational injury, and include phosgene (CG), diphosgene (DP), chlorine (CL), chloropicrin (PS) and perfluoroisobutene (PFIB). Lung damaging agents are also sometimes called choking agents and pulmonary agents.

**Nerve agents:** A class of organophosphorus compounds that are used as CW agents. Nerve agents affect the transmission of nerve impulses in the nervous system. They are stable and easily dispersed, extremely toxic and have rapid effects both when absorbed through the skin and via respiration. There are two classes of nerve agents: the G-series nerve agents which include tabun (GA), sarin (GB), soman (GD) and cyclohexyl-sarin (GF); and the V-series nerve agents which include VX and Vx. The V-series are considerably less volatile and more persistent than the G-series nerve agents.

**NSTX:** Neosaxitoxin - *see STX Saxitoxin.*

**OC:** Oleoresin capsicum. *See Riot Control Agents.*

**OPs:** Organophosphorus compounds. These are organic chemicals that contain one or more atoms of phosphorus in each molecule.

**OPIDN:** Organophosphorus induced delayed neuropathy.

**PaCO<sub>2</sub>:** Partial pressure of arterial carbon dioxide.

**PaO<sub>2</sub>:** Partial pressure of arterial oxygen.

**PAP:** Positive airway pressure.

**PCR:** Polymerase chain reaction.

**PEEP:** Positive end-expiratory pressure.

**PFIB:** Perfluoroisobutene. *See lung damaging agents.*

**PPE:** Personal protective equipment: PPE is the first line of defence in a chemical-contaminated environment that comprises a respirator and protective clothing, including suitable gloves and boots.

**Precursor:** Starting material for the production of, for example, CW agents.

**PSP:** Paralytic shellfish poisoning. *See Saxitoxin*

**PST:** Paralytic shellfish toxin. *See Saxitoxin*

**PTSD:** Post-traumatic stress disorder.

**RCA:** Riot Control Agent: A sensory irritant chemical that is capable, when used in field concentrations, of rapidly causing temporary disablement that lasts for little longer than the period of exposure. Sometimes also called harassing agents.

**Ricin:** A highly toxic compound that can be extracted from castor beans. Ricin consists of two peptide chains, RTA and RTB, which are linked by a disulphide bond. RTB binds to the cell wall to facilitate entry of ricin into the cell, and RTA inhibits protein synthesis.

**RSDL:** Reactive skin decontamination lotion kit.

**RTA:** Chain A of ricin toxin. *See Ricin*

**RTB:** Chain B of ricin toxin. *See Ricin*

**SAB:** Scientific Advisory Board (of the OPCW).

**SCBA:** Self-contained breathing apparatus.

**STX:** Saxitoxin is a non-protein toxin produced by marine algae (dinoflagellate *Gonyaulax catanella*), that are in turn ingested by shellfish, including clams and mussels. It is one of the most potent natural toxins known to man. The term saxitoxin can also refer to the entire suite of related neurotoxins that are known collectively as

saxitoxins, which include saxitoxin (STX), neosaxitoxin (NSTX) and gonyautoxin(GTX). These toxins cause paralytic shellfish poisoning (PSP) and are sometimes referred to as paralytic shellfish toxin (PST).

**TIC:** Toxic industrial chemical.

**Triage:** The process of determining the priority of patients' treatments based on the severity of their condition.

**Vesicant:** *See Blister agents*

**VX:** Military code for the nerve agent *O-ethyl-S-[2(diisopropylamino)ethyl]methylphosphonothioate*. *See Nerve agents.*

## Authors' biographies

### **Prof. Mahdi Balali-Mood MD PhD FTWAS**



Mahdi Balali-Mood obtained his BSc. (1<sup>st</sup> class Hon.) in chemistry in 1963 and MD in 1970 from Tehran University. After earning his PhD in Clinical Pharmacology and Toxicology at Edinburgh University Medical School in 1981, he was working as a lecturer there until winter 1982, when he returned to Mashhad, where he was promoted to Associate Professor and Full Professor of Medicine and Clinical Toxicology at Mashhad University Medical Sciences in 1984 and 1988, respectively.

Prof. Balali-Mood has served as a Clinical Toxicology Adviser to WHO since 1989. He was a founding member and President of Iranian Society of Toxicology (1970-2001) and also co-founder and President of Asia-Pacific Association of Medical Toxicology (1994-2001). Mahdi was elected as a permanent fellow of The World Academy of Sciences in 1997. He has collaborated with OPCW since 2004. Prof. Balali-Mood was awarded 16 prizes. He is author/editor of 452 articles, 39 chapters/books and 3 journals.

**Dr Robert (Bob) Mathews DSc OAM FRACI**



Robert (Bob) Mathews is Head of the NBC Arms Control Unit at the Australian Defence Science and Technology Organisation (DSTO), and an honorary Associate Professor at the University of Melbourne Law School.

He spent his early years at DSTO undertaking scientific research in the detection and analysis of chemical warfare agents, including 6 years of international collaboration with UK, USA and Canada on the development of the Chemical Agent Monitor (CAM). He served as Scientific Adviser to the Australian Delegation to the UN Conference on Disarmament in the negotiation of the Chemical Weapons Convention (CWC) in Geneva from 1984, and since 1993 has provided scientific support to the Australian delegation to the Organisation for the Prohibition of Chemical Weapons (OPCW), based in The Hague.

He has also provided support to Australia's efforts towards non-proliferation of weapons of mass destruction, including the efforts to strengthen the Biological Weapons Convention (BWC).

**Dr René Pita**



Dr René Pita is head of the Chemical Defence Department at the Army NBC Defence School, Madrid, Spain. He holds a Ph.D. in neurotoxicology from Madrid Complutense University.

Dr Pita has more than 20 years of experience in the strategic, operational, and tactical aspects of CBRN defence, including different NATO and Proliferation Security Initiative (PSI) exercises.

He has written and given lectures extensively on issues of chemical defence and collaborates in training courses organised by the OPCW's Assistance and Protection Branch.

**Dr. Paul Rice OBE BM FRCPath FRCP FRSB**



Dr. Paul Rice graduated in medicine from Southampton University Medical School in June 1982. He then trained to Consultant level in histopathology and toxicology, gaining Membership of the Royal College of Pathologists in 1993. Since then he has been made a Fellow of the Royal College of Pathologists in 2003, was made a special Fellow of the Royal College of Physicians in 2007 and appointed as a Fellow of the Royal Society of Biology in 2010.

Today as Chief Medical Officer at Dstl Porton Down, he provides UK MoD with a focus for advice on matters of medicine and clinical toxicology, including the preparation of answers to Parliamentary Questions, drafting briefing notes for Ministers, and interacting with the media on a range of topics including chemical & biological defence, the ethics of human experimentation and the use of animals in research. He has in the past presented expert testimony on the toxicological and medical consequences of the use of tear gases to the US Congress and continues to provide scientific and medical advice to the UK Home Office and Department of Health on matters of chemical and biological defence and CB counter-terrorism.

### **Dr James Romano**



COL (ret.) Romano is a board-certified toxicologist who has worked extensively in the areas of pharmacology/toxicology in support of drug development. He had served nearly 30 years in the US Army, all of it involved in conducting, managing, contracting for, and reporting on military medical research projects.

COL (ret.) Romano rose through the ranks to command the US Army Medical Research Institute for Chemical Defence, the US Army's lead laboratory for medical chemical defence. He also commanded the US Army Medical Research and Materiel Command, Fort Detrick, Frederick, MD, a world-wide command of over 6,000 military, civilian, and contractor personnel. In the latter position he was responsible for all areas of Army medical research, as well as medical logistics for field units in Southwest Asia.

Dr Romano received his Ph.D. from Fordham University and served as a tenured Assistant Professor at Manhattan College, Riverdale, NY prior to entry onto active duty.

### **Prof. Horst Thiermann MD**



Colonel (MC) Prof. Dr. Horst Thiermann studied medicine at the University of Regensburg and Technical University, Munich. After working in the Bundeswehr Hospital Munich in the departments of anaesthesiology and surgery, he changed to the Bundeswehr Institute of Pharmacology and Toxicology. He specialised in Pharmacology and Toxicology at the Walther-Straub-Institute of Pharmacology and Toxicology, Ludwig Maximilians-University Munich in 1996. In 2002, he completed his advanced studies of Clinical Pharmacology at MDS Pharma Services, Höhenkirchen-Siegertsbrunn.



Since November 2006 he is in charge of the Bundeswehr Institute of Pharmacology and Toxicology. In January 2012 he was appointed Professor at Technical University, Munich.

Colonel (MC) Prof. Dr. Thiermann is vice-chairman of Bundesinstitut für Risikobewertung (BfR) Committee for the Assessment of Intoxications, member of the board and scientific committee of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and president of Clinical and Translational Toxicology Speciality Section (CTTSS) of the Society of Toxicology (SOT).

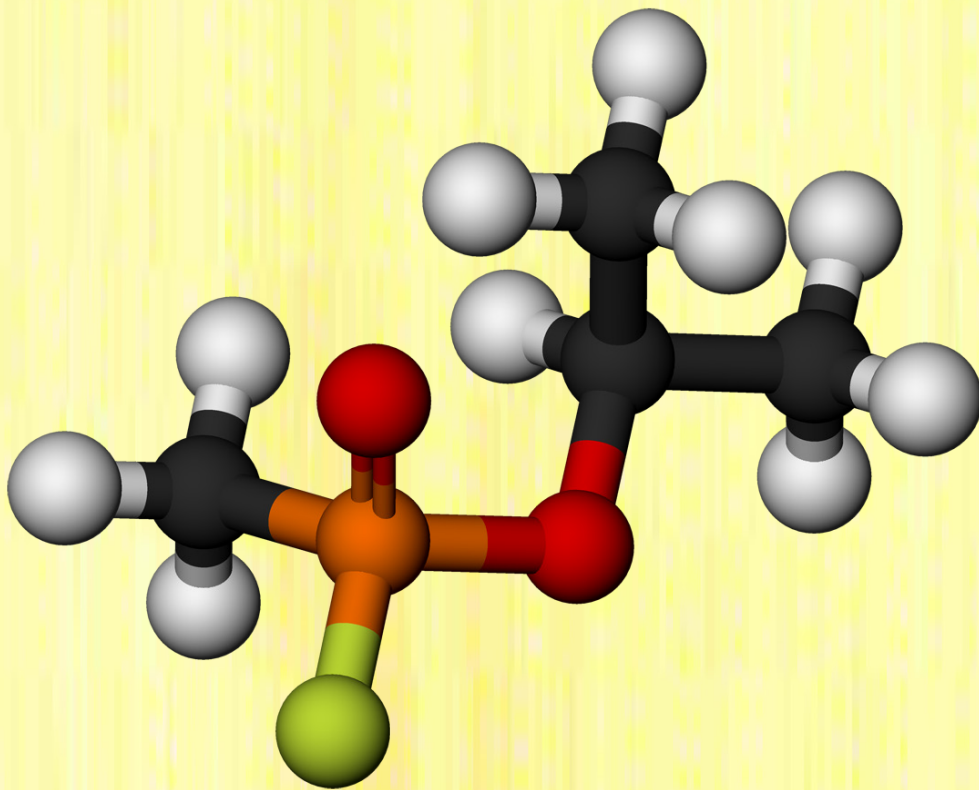
### **Jan Leo Willems MD PhD**



Dr Willems graduated in medicine (1964) and obtained a PhD in pharmacology (1974) from Ghent University Medical School. He was active in the fields of pharmacology, toxicology and environmental health, both in the Belgian Military Medical Services and at the University.

He assumed several functions in the Department of NBC Defence of the Belgian Armed Forces and, later on, in the Royal School of the Military Medical Services, which he left as commander in 1995. At the university he became interested in organophosphate pesticide poisoning and in clinical management of sulphur mustard casualties. He retired from university in 2004 as professor of environmental health.

As member and chairman of several working groups of the Belgian Health Council, He became involved in pesticide registration and in chemical safety. He was invited to participate in a UN chemical weapons verification mission, in UNSCOM and to give advice to the OPCW.



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