SECOND EDITION

HANDBOOK OF TOXICOLOGY OF CHEMICAL WARFARE AGENTS

EDITED BY

RAMESH C. GUPTA

HANDBOOK OF TOXICOLOGY OF CHEMICAL WARFARE AGENTS

THE UNCERTAINTY OF THE DANGER BELONGS TO THE ESSENCE OF TERRORISM

Jürgen Habermas (1929–Present)

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON
NEW YORK • OXFORD • PARIS • SAN DIEGO
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Academic Press is an imprint of Elsevier

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32 Jamestown Road, London NW1 7BY, UK
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA
225 Wyman Street, Waltham, MA 02451, USA
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK

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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-800159-2

Typeset by MPS Limited, Chennai, India
www.adi-mps.com

Printed and bound in United States of America

Dedication

This book is dedicated to my beloved wife Denise, daughter Rekha,
and parents, the late Chandra and Triveni Gupta

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SECTION I

INTRODUCTION, HISTORICAL PERSPECTIVE, AND EPIDEMIOLOGY

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CHAPTER

1

Introduction

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For centuries, extremely toxic chemicals have been used in wars, conflicts, terrorist and extremist activities, malicious poisonings, and executions. Natural toxins from plants or animals were one of the earliest forms of chemical warfare agents (CWAs). These were used to coat arrowheads and were commonly referred to as "arrow poisons." Ancient use of some CWAs and riot control agents (RCAs) dates back to the fifth century BC, during the Peloponnesian War, when the Spartans used smoke from burning coal, sulfur, and pitch to temporarily incapacitate and confuse occupants of Athenian strongholds. The Spartans also used bombs made of sulfur and pitch to overcome the enemy. The Romans used irritant clouds to drive out adversaries from hidden dwellings. In the fifteenth century, Leonardo da Vinci proposed the use of an arsenic sulfide powder as a chemical weapon. Modern use of CWAs and RCAs or incapacitating agents dates back to World War I (WWI).

With advancements in science and chemistry in the 19th century, the possibility of chemical warfare increased tremendously. The first full-scale use of CWAs began in April 1915, when German troops launched a poison gas attack in Ypres, Belgium, using 168 tons of chlorine gas, killing approximately 5000 Allied (British, French, and Canadian) soldiers. During WWI, the deployment of CWAs, including toxic gases (chlorine, phosgene, cyanide, and mustard), irritants, and vesicants in massive quantities (approximately 125,000 tons), resulted in approximately 90,000 fatalities and 1.3 million nonfatal casualties. The majority of deaths during WWI were a result of exposure to chlorine and phosgene gases. During the Holocaust, the Nazis used carbon monoxide and the insecticide Zyklon-B, which contains hydrogen cyanide, to kill several million people in extermination camps. Poison gases were also used during the Warsaw Ghetto Uprising in 1943. In November 1978, religious cult leader Jim Jones murdered more than 900 men, women, and children with cyanide.

Before, during, and after World War II, anticholinesterase organophosphate (OP) nerve agents/gases were developed in Germany, the United States, the United Kingdom, and Russia. They were also produced in large volumes in many other countries. During the "Cold War" period, they were maximally produced and stockpiled. These nerve agents have been used in wars and by dictators, extremists, cult leaders, and terrorist groups as chemical weapons of mass destruction (CWMD) on many occasions. In 1980, Iraq attacked Iran using mustard gas and OP nerve gas. During the period of the Iraq and Iran conflict (1980–1988), Iran sustained 387 attacks and more than 100,000 troops were victims, as were a significant number of civilians. Thousands of victims still suffer from long-term health effects. Soon after the end of the Iraq–Iran war in 1988, the brutal dictator of the Iraqi regime, Saddam Hussein, used multiple CWAs against the Kurdish minorities in a Halabja village, killing more than 10% of the town's 50,000 residents. To date, mustards have been used in more than a dozen conflicts, killing and inflicting severe injuries in millions of military personnel and civilians.

During the Persian Gulf War, exposure to OP nerve agents occurred from the destruction of munitions containing 8.5 metric tons of sarin/cyclosarin housed in Bunker 73 at Khamisyah on March 4, 1991, and during additional destruction of these nerve agents contained in rockets in a pit at Khamisyah on March 10, 1991. Although exposure levels to nerve agents were too low to produce signs of acute toxicity, military personnel serving in and around the Khamisyah area still suffer from long-term adverse health effects, most notably "Gulf War Syndrome." In 1996, approximately 60,000 veterans of the Persian Gulf War claimed to suffer from "Gulf War Syndrome" or "Gulf Veterans' Illnesses," possibly because of low-level exposure to nerve agents, mustard, pyridostigmine bromide, and pesticides. Exposed veterans had an increased incidence of chronic

Handbook of Toxicology of Chemical Warfare Agents.
DOI: http://dx.doi.org/10.1016/B978-0-12-800159-2.00001-4

myelocytic leukemia and increased risk of brain cancer deaths compared with unexposed personnel.

In the mid 1990s, two terrorist attacks by a fanatic religious cult Aum Shinrikyo (Supreme Truth), known as Aleph since 2000, took place in Japan (Matsumoto in 1994 and Tokyo Subway in 1995). In both incidents, the OP nerve agent sarin was used as a CWA. An estimated 70 tons of sarin was manufactured by Aum Shinrikyo in Kamikuishiki, Japan. Although the total fatality count involved not more than 20 civilians, injuries were observed in more than 6000 and millions were terrified. These acts of chemical terrorism were unprecedented and the impact propagated not only throughout Japan but also throughout the entire world. In the past few decades, many incidents have also occurred with biotoxins such as ricin and anthrax. Publicity surrounding frequent recent use attributable to easy access and copycat crimes increase the possibility of future use of these chemicals and biotoxins, thus warranting advancement in emergency preparedness planning at the federal, state, and local government levels.

It is interesting to note that toxic chemicals have been used by governmental authorities against rebels or civilians. In the 1920s, Britain used chemical weapons in Iraq "as an experiment" against Kurdish rebels seeking independence. Winston Churchill strongly justified the use of "poisoned gas against uncivilized tribes." The Russian Osnaz Forces used an aerosol containing fentanyl anesthetic during the Moscow theater hostage crisis in 2002. RCAs were frequently used in the United States in the 1960s to disperse and control crowds.

At present, more than 25 countries and possibly many terrorist groups possess CWAs, and many other countries and terrorist groups are seeking to obtain them because of their easy access. Some of these agents are stockpiled in enormous quantities and their destruction and remediation are not only expensive but also associated with significant health risks. There is also the possibility of accidental release of CWAs or CWMD at the sites of their production, transportation, dissemination, and deployment. The intentional or accidental release of highly toxic chemicals, such as the nerve agent VX (Dugway Proving Ground, Utah, USA, 1968), Agent Orange (Vietnam, 1961–1972), PBB (Michigan, USA, 1973), dioxin (Seveso, Italy, 1976), and methyl isocyanate (Bhopal, India, 1984), has caused injuries in more than one million people and deaths in several thousands. A 1968 accident with VX nerve gas killed more than 6000 sheep in the Skull Valley area of Utah.

After September 11, 2001, the chances for the use of CWMD by extremist and terrorist groups, such as Al Qaeda, have been greater than ever, thus presenting great risks to humans, domestic animals, and wildlife in many parts of the world. On November 26, 2008, Pakistani Islamic terrorists attacked Mumbai City in India at 10 different sites, including two luxury hotels, a Jewish center, a train station, hospitals, and cafes. Approximately 200 innocent people died and approximately 300 people were injured by bullets and smoke. It is more likely that terrorist groups such as these may use toxic industrial chemicals (agents of opportunity) either in this way or as a precursor for more deadly CWMD. At present, many countries have established Defense Research Institutes with two major missions: (i) to understand the toxicity profile of CWAs/CWMDs and (ii) to develop strategic plans for prophylactic and therapeutic countermeasures. By the turn of the twenty-first century, the United States established the Department of Homeland Security. Many other countries also developed similar governing branches and agencies at the state and national levels to protect people and property from terrorist attacks. Among chemical, biological, and radiological weapons, the possibility of CWMD is more likely because of their easy access and delivery system. It is important to mention that understanding the toxicity profile of CWAs/CWMD is very complex, because these chemical compounds are of a diverse nature and, as a result, treatment becomes very difficult or, in some cases, impossible.

In the past, many accords, agreements, declarations, documents, protocols, and treaties have been signed at the international level to prohibit the development, production, stockpiling, and use of CWAs, yet dictators and terrorists produce and/or procure these chemicals to harm or kill enemies, create havoc, and draw national and international attention. In 1907, The Hague Convention outlawed the use of chemical weapons; however, during WWI, many countries used these chemicals. The first international accord on the banning of chemical warfare was agreed upon in Geneva in 1925. Despite the General Protocol, the Japanese used chemical warfare against China in 1930. In 1933, the Chemical Weapon Convention banned the development, possession, and use of CWAs. The document was signed and implemented by more than 100 countries. However, during WWII many chemicals of warfare were developed, produced, and used by several countries. In 1993, another global convention banning the production and stockpiling of CWAs was signed by more than 100 countries.

It is highly likely that these agents will be used in wars, conflicts, and terrorist attacks with malicious intent. In such scenarios, these extremely toxic agents continuously pose serious threats.

This first edition of *Handbook of Toxicology of Chemical Warfare Agents* was prepared to offer the most comprehensive coverage of every aspect of the deadly toxic chemicals that can be used as CWAs/CWMD. In addition to the chapters on radiation, several chapters were included on deadly biotoxins (ricin, abrin, strychnine, anthrax, and botulinum toxins) that can be weaponized in chemical, radiological, and biological warfare. Many

special and unique topics were offered that were not covered in other books. This was the first book to offer detailed target organ toxicity in the area of toxicology. In every chapter, all factual statements were substantiated with appropriate references.

Since the publication of the first edition of this handbook, concerns regarding the use and misuse of CWAs and biological warfare agents (BWAs) are greater than ever before. The delayed health effects from CWAs used during the Iraq–Iran conflict of the 1980s, during the sarin subway attacks in Japan and during the first Gulf War in the 1990s are still not well-understood. Recently, the Syrian government stockpiled more than 1300 metric tons of chemical agents, including sarin, VX, and sulfur mustard. In August 2013, the Syrian military repeatedly attacked civilians with chemical weapons, including sarin. More than 1300 people died and thousands were injured. Again, during April 11–13, 2014, Syrian military forces attacked civilians in Hama province with chlorine gas, killing and injuring an unaccounted number of people. Of course, the Syrian government has denied use of either sarin or chlorine gas.

The second edition of the *Handbook of Toxicology of Chemical Warfare Agents* is prepared to meet today's challenges of academicians and lay persons alike. The format used is user-friendly and easy to understand. Standalone chapters on individual chemical and biological agents, target organ toxicity, biosensors and biomarkers, risks to humans, animals, and wildlife, and prophylactic and therapeutic countermeasures are just a few of the many novel topics covered in this volume. The chapters are enriched with historical background as well as the latest information and up-to-date references. With 76 chapters, this book serves as a reference source for biologists, toxicologists, pharmacologists, forensic scientists, analytical chemists, local/state/federal officials in the Department of Homeland Security, Department of Defense, Defense Research Establishments, Department of Veterans Affairs, physicians at medical and veterinary emergency care units of hospitals, poison control centers, medical and veterinary diagnostic laboratories, environmentalists and wildlife interest groups, researchers in the areas of nuclear, chemical, and biological agents, and college and university libraries.

Contributors to the chapters in this book are the most qualified scientists in their particular areas of CWAs and BWAs. These scientists are from around the globe and are regarded as authorities in the fields of pharmacology, toxicology, and military medicine. The editor sincerely appreciates the authors for their dedicated hard work and invaluable contributions to this volume. The editor gratefully acknowledges Robin B. Doss and Michelle A. Lasher for their technical assistance. Finally, the editor remains indebted to Molly McLaughlin, Rhys Griffiths, and Kristine Jones, the editors at Elsevier, and Caroline Johnson, Susan McClung and Heather Turner in the production department of Elsevier for their immense contributions to this book.

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CHAPTER

2

Historical Perspective of Chemical Warfare Agents

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The opinions and assertions contained herein are the private views of the authors, and are not to be construed as reflecting the views of the US Department of Defense, the US Air Force, or the US Department of Health and Human Services.

INTRODUCTION

The employment of chemicals in war has a long history (Silvagni et al., 2002; Romano et al., 2008). Just as the use of chemicals brought about tremendous advances in society, the concept of using chemicals to help win wars has been pursued for centuries (Joy, 1997; Smart, 1997). There are many examples of the exploitation of chemicals in warfare and conflict dating back to ancient times. Primitive humans may have been the first to use chemical compounds in both hunting and battle scenarios. The use of smoke from fires to drive animals or adversaries from caves may have been the earliest use of chemical weapons. Natural compounds derived from plants, insects, or animals that were observed to cause sickness or death were likely used by our distant ancestors in attempts to gain or maintain superiority (Hammond, 1994). Natural toxins from plants or animals on arrowheads, as well as the poisoning of water or food, could increase casualties and cause fear in opposing military forces or civilian populations. These early uses of chemicals paved the way for more lethal chemical weapons. For example, in the fourth century BC, smoke containing sulfur was used in the war between Sparta and Athens (Joy, 1997). Chinese manuscripts indicate arsenic-based compounds were used in battle (Joy, 1997). A few hundred years later, toxic smoke was employed by the Romans in Spain (Coleman, 2005). During the second siege of Constantinople, the Byzantine emperor Leo III used "Greek fire" in his quest for military victory (Coleman, 2005). During the ensuing years, there were many instances of the limited and attempted use of chemicals and toxins on the battlefield. Many of these examples may have been influenced by the intentional poisonings occurring in civilian settings (Joy, 1997; Smart, 1997; Newmark, 2004; Coleman, 2005). The earliest known treaty to ban poisons in warfare was signed between the French and Germans in the seventeenth century (Smart, 1997). In the siege of Groningen, European armies employed incendiary devices to release belladonna, sulfur, and other compounds. This led to the Strasbourg Agreement in 1675, which prohibited poison bullets (Smart, 1997; Coleman, 2005).

As science and chemistry advanced in the nineteenth century, the possibilities of chemical warfare increased exponentially. Advancements were made in industrial applications of sulfur, cyanide, and chlorine (Joy, 1997). In addition, the concept of delivering chemicals via projectiles was introduced. During the Crimean War, the British refused to use cyanide-based artillery shells against the Russians on the grounds that it was a "bad mode of warfare" (Smart, 1997). This was an early example of the ethical questions surrounding chemical use in warfare that continued into the twentieth century (Vedder and Walton, 1925). During the US Civil War, both the Northern and Southern armies seriously considered using various chemicals in their pursuit of operational victories (Smart, 1997). Early attempts at international treaties met with mixed results. The United States prohibited any use of poison during the Civil War. The Brussels Convention on the Law and Customs of War of 1874 prohibited poisons or poison-related arms (Smart, 1997). The first Peace Conference at the Hague

Handbook of Toxicology of Chemical Warfare Agents.
DOI: http://dx.doi.org/10.1016/B978-0-12-800159-2.00002-6

prohibited projectiles filled with asphyxiating or deleterious gases (Smart, 1997). The employment of chemicals as asphyxiating warfare agents was vigorously discussed there (Joy, 1997). However, some countries, including the United States, were not signatories to this agreement. Arguments again were made against chemicals based on moral grounds. However, counterarguments were made based on the assumption that chemicals lead to death without suffering (Vedder and Walton, 1925; Joy, 1997; Coleman, 2005). Individuals who advocated chemicals did not view their use as an unfair advantage; rather, it was just one of a series of technological advances which, if mastered, could provide strategic, operational, and tactical advantages on the battlefield. The second Peace Conference at the Hague, held eight years later, prohibited both poisons and poisoned weapons (Smart, 1997). The British use of picric acid–filled shells during the Boer War and the Japanese use of arsenical rag torches in the Russo-Japanese War further illustrate that chemical warfare was considered by some a legitimate form of warfare at the turn of the twentieth century (Smart, 1997). During the early twentieth century, technological advancements in the chemical industry made the possibility of sustained military operations using chemicals a realistic possibility. The murder of Archduke Franz Ferdinand at Sarajevo in June 1914, which sparked World War I, set the stage for what would become the first widespread use of chemical weapons to date (Harris and Paxman, 2002).

THE FIRST SUSTAINED USE OF CHEMICALS AS AGENTS OF WAR

The talk and rhetoric of the late nineteenth century should have prepared the countries on both sides of World War I for chemical warfare. However, that was not the case (Smart, 1997). World War I clearly demonstrated the deadly and destructive nature of chemicals in modern warfare. Both sides of the war experimented with novel forms of warfare, including chemical weapons, and followed the lead of their adversary (Hay, 2000). It is little wonder that this war is known as the "chemist's war" (Fitzgerald, 2008). Initially, the French used gas grenades with little effect, followed by the German use of shells filled with tear gas (Joy, 1997). The Germans, capitalizing on their robust chemical industry, produced shells filled with dianisidine chlorosulfate (Smart, 1997). These shells were used in October 1914 against the British at Neuve-Chapelle, but with little effect. In the winter of 1914–1915, the Germans fired 150-mm howitzer shells filled with xylyl bromide (Smart, 1997). These shells were fired on both the eastern and western fronts, with disappointing effects. Despite this inauspicious start, efforts were continued to develop new uses of chemical warfare. It would soon be evident that chemical weapons would be devastating on the battlefield (Coleman, 2005; Tucker, 2006). In late 1914, Fritz Haber, a German scientist who later won the Nobel Prize in Chemistry, proposed the possibility of releasing chlorine gas from cylinders (Joy, 1997). Chemical warfare was attractive to Germans for two reasons: the shortage of German artillery shells and the ability to defeat the trench system of the enemy (Smart, 1997). After consideration and debate, the Germans released chlorine in April 1915 at Ypres, Belgium (Coleman, 2005). The German military was not prepared for the tremendous operational advantage the chlorine release provided, however. It did not take long for the British and French forces to respond in kind to the German offensive (Vedder and Walton, 1925; Joy, 1997; Smart, 1997; Coleman, 2005). In the fall of 1915, a British officer, William Livens, introduced a modified mortar (Figure 2.1) that could project gas-filled shells of chlorine or phosgene, the two agents of choice at that time (Joy, 1997). Both chlorine and phosgene caused extreme respiratory problems to those soldiers who were exposed to them (Vedder and Walton, 1925; Joy, 1997; Smart, 1997; Coleman, 2005; Hurst et al., 2007) (Figure 2.2).

FIGURE 2.1 British Livens Projector, western front, World War I.

As the United States entered the war in the spring of 1917, an obvious concern of its military command was the effect of chemical warfare on standard operations. Chemistry departments at universities were tasked with investigating and developing novel chemical agents (Joy, 1997). Protective equipment (Figure 2.3) and basic studies of the biological effects of chemical agents were assigned to the US Army Medical Department (Joy, 1997). In the fall of 1917, the army began to build an industrial base for producing chemical agents at Edgewood Arsenal, MD (Joy, 1997). As the effects of chlorine and phosgene became diminished by the advent of gas masks (Figure 2.4), the Germans turned to dichlorethyl sulfide (mustard) at Ypres against the British (Joy, 1997). As opposed to the gases, mustard remained persistent in

FIGURE 2.2 Australian infantry in trench with gas masks donned, Ypres, Belgium, September 1917.

FIGURE 2.3 US Army captain wearing a gas mask in training, 1917.

the area, and contact avoidance was the major concern (Joy, 1997). It is worth noting that almost 100 years after it was first used on the battlefield, mustard still has no effective treatment; research continues into developing effective therapeutics (Babin et al., 2000; Baskin et al., 2000; Casillas and Kiser, 2000; Hay, 2000; Schlager and Hart, 2000; Hurst et al., 2007; Romano et al., 2008). It has been estimated that there were over 1 million chemical casualties (Figure 2.5) of World War I, with almost 8% being fatal (Joy, 1997). The Russians on the eastern front had a higher percentage of fatalities than other countries in the war, primarily due to the later introduction of a protective mask (Joy, 1997). The relatively low rate of chemical deaths in World War I demonstrated the most insidious aspect of the use of such weapons—namely, the medical and logistical burden that it placed on the affected army. The eventual Allied victory brought a temporary end to chemical warfare. In 1919, the Treaty of Versailles prohibited the Germans from producing or using chemical weapons.

FIGURE 2.4 World War I soldier and horse, both wearing gas masks.

FIGURE 2.5 British soldiers temporarily blinded by tear gas awaiting treatment at the Battle of Estaires, April 1918.

INITIAL COUNTERMEASURES

The concept of a protective mask against chemical attack dates back over 500 years, to Leonardo da Vinci (Smart, 1997). By the mid-nineteenth century, protective masks were proposed in the United States and Europe for both industrial and military use. The modern gas mask was developed by the Germans with sodium thiosulfate- and bicarbonate-soaked pads, and it was used during World War I (Joy, 1997). The French and English soon followed with their own versions of gas masks (Joy, 1997). In 1916, the Germans introduced a mask that incorporated a canister through which the soldiers breathed (Joy, 1997). Initially, the American forces in World War I used gas masks obtained from allies already fighting in the war (Smart, 1997). In 1918, the Americans introduced Richardson, Flory, and Kops (RFK) mask, a modified version of the British mask. In addition, masks were developed for the animals, such as horses, that supported the war efforts. Decontamination efforts during World War I were rudimentary and included chemical neutralization and aeration of clothing and equipment. Although the need to detect chemical agents was clearly identified, very little progress was made during World War I. Medical treatment included removal of the patient from the source, decontamination, and palliative care (Smart, 1997).

EVENTS AFTER WORLD WAR I

By the time World War I ended, the world had been introduced to chemical warfare on an unprecedented level. While some groups thought that humanity had learned a lesson about the cruel nature of chemical warfare, others prudently went to work on improving chemical defenses (Vedder and Walton, 1925). The thoughts of many professional military officers were that future wars would be fought under the new paradigm of chemical warfare (Vedder and Walton, 1925; Vedder, 1926; Smart, 1997). New gas masks were developed, and training in chemical environments was introduced (Vedder and Walton, 1925; Vedder, 1926; Joy, 1997). Textbooks and manuals, such as those written by US Army Colonel Edward B. Vedder (Figure 2.6), were introduced into the military medical community (Vedder and Walton, 1925). In addition, the civilian medical community gained valuable insight into toxicology from the events of World War I (Vedder, 1929; Johnson, 2007). Despite the firsthand experience with chemical warfare, some countries, including the United States, struggled to fund their offensive and defensive programs adequately during demobilization (Smart, 1997).

It did not take long for chemical warfare to appear in other conflicts. Chemical agents were used to subdue rioters and suppress rebellions. For example, the British used chemical agents to suppress uprisings in Mesopotamia in the early 1920s by dropping bombs in cities throughout the area (Coleman, 2005). The Soviet Union used chemical agents to quell the Tambov peasant rebellion in 1921, and France and Spain used mustard-gas bombs to subdue the Berber rebellion in the 1920s (Werth et al., 1999). Italy and Japan used mustard in several small regional conflicts (Joy, 1997). The Italian conflict in Ethiopia was particularly noteworthy because mustard was sprayed and dropped from planes, and some experts think that the agent's use contributed significantly to the Italian victory (Smart, 1997). This use demonstrated the contemporary belief that chemicals were viable alternatives to traditional combat.

FIGURE 2.6 Captain Edward B. Vedder, the "father" of the United States Army Medical Research Institute of Chemical Defense (USAMRICD).

The Japanese also used chemical weapons during the 1930s against regional foes. Mustard gas and the vesicant lewisite were released against Chinese troops and were also used in Southeast Asia (Coleman, 2005). Lewisite is an arsine that was usually produced as an oily brown liquid that was said to smell like geraniums (Spiers, 1986; Hammond, 1994). It was developed in the United States by Winford Lee Lewis in 1918 and was found to be effective at penetrating clothing. The United States produced approximately 20,000 tons of lewisite but only used small quantities of the chemical in World War I (Coleman, 2005). Dimercaprol, more commonly called *British antilewisite*, was developed as an effective treatment for the vesicant (Goebel, 2008). In the period between the two world wars, mustard was a key part of defensive planning (Coleman,

2005). New stores of mustard were produced in many countries. Work continued on many fronts to improve protective equipment. For example, the US Chemical Warfare Service introduced the M1A2 mask, an improvement on the M1 mask (Smart, 1997). In the Geneva Protocol of 1925, 16 of the world's major nations pledged never to use gas as a weapon of warfare; however, it was not ratified in the United States until 50 years later, in 1975 (Hammond, 1994). There has long been vigorous debate on the merits of treaties with nations that balance military needs against the potential irrational concept of chemical warfare (Vedder, 1926).

WORLD WAR II

In the lead-up to World War II, the Germans forever changed chemical warfare with the discovery of the organophosphorus nerve agents (Goebel, 2008). These agents inhibit cholinesterase enzymes in the nerve synapse responsible for the breakdown of the neurotransmitter acetylcholine (ATSDR, 2008). This results in the accumulation of the neurotransmitter in the synapse and overstimulation of the nervous system. This can result in subsequent respiratory failure and death (ATSDR, 2008).

In 1936, Gerhard Schrader, a German chemist working on the development of insecticides for IG Farben, developed a highly toxic organophosphate compound, which he named *tabun* (Hersh, 1968; Hammond, 1994). Schrader and an assistant became casualties of their discovery when a drop of the neurotoxicant was spilled in the lab, exposing both of them (Tucker, 2006). Had the amount of tabun spilled been greater, both researchers would have certainly succumbed to the effects of the poison. Tabun was the first of a series of compounds termed *nerve gases* (Coleman, 2005). The correct terminology, however, is *nerve agents*, as these substances are not gases; rather, they are liquids dispersed as fine aerosols. Tabun was extremely toxic in small amounts, and it was invisible and virtually odorless (Tucker, 2006). The compound could be inhaled or absorbed through the skin. These characteristics made it too dangerous to be used as an insecticide by farmers. German law required that any discovery having potential military applications be reported to military officials (Tucker, 2006). Schrader was not overly excited about producing chemical agents for the military; however, the Germans placed him in a secret military research facility with the emphasis on producing these nerve agents and discovering new agents (Tucker, 2006). Subsequently, Schrader and his team of researchers discovered a more lethal organophosphate compound similar to tabun, which he named *sarin* in honor of the team members: Schrader, Ambrose, Rudriger, and van der Linde (Coleman, 2005).

FIGURE 2.7 Gas mask production—Detroit, Michigan, 1942.

FIGURE 2.8 A private trains using protective gear during World War II.

At the onset of World War II, both the Allies and the Germans anticipated that chemical agents would be deployed on the battlefield (Tucker, 2006). This expectation intensified research into the development of new agents, delivery systems, and methods of protection (Figures 2.7 and 2.8). The Allied forces were unaware of the Germans' new nerve agent, tabun, at the beginning of the war. The German Army advanced very rapidly across Europe using their Blitzkrieg method of maneuvering. As a result, German military leaders were reluctant to use chemical weapons, fearing that their forces would lose momentum waiting for contaminated areas

to clear. (Tucker, 2006). Nevertheless, the Germans produced and stockpiled large amounts of nerve agents throughout the war (Spiers, 1986). The production of these organophosphate agents was complex, required custom equipment, and was hazardous to those involved in its production (Tucker, 2006). If workers got exposed, they would be dunked in a bath of sodium bicarbonate (Harris and Paxman, 2002; Goebel, 2008). It is also interesting to note that some members of the German workforce were given rations containing higher percentages of fat (Harris and Paxman, 2002). This was done because authorities observed that workers with higher-quality rations seemed protected against exposure to low levels of tabun. Many detainees were used in the manufacture and testing of chemical agents in Germany (Harris and Paxman, 2002; Tucker, 2006). It is not known how many chemical casualties resulted from prisoners of war being forced to work at producing nerve agents, but some fatalities were documented. The discovery of tabun and sarin was followed by the discovery of soman in 1944 by Richard Kuhn and Konrad Henkel at the Kaiser Wilhelm Institute for Medical Research (Tucker, 2006). This class of nerve agents is collectively termed "G" agents; the *G* stands for *German*, since German researchers discovered this class of compounds. A second letter is included as the specific identifier of each compound: GA (tabun), GB (sarin), GD (soman), and GF (cyclosarin) (ATSDR, 2008). These agents were mass-produced by the Nazi regime throughout the war, but they were not used (Tucker, 2006). There has been considerable debate about why the Germans did not employ their chemical weapons in World War II. While it may never be known conclusively, several possible reasons include lack of intelligence regarding the German superiority in chemical weapons, fear of retaliation, and Adolf Hitler's personal exposure to chemical agents on the battlefield in World War I (Harris and Paxman, 2002; Tucker, 2006).

Other chemical agents that had been produced during and following World War I were still being produced. On December 2, 1943, German planes sank several American ships off the coast of Italy. At least one of the ships contained mustard, which was to be used in retaliation if the Germans unleashed a large-scale chemical weapons attack (Tucker, 2006). Many casualties resulted from exposure to the mustard, some of which included civilian merchant seamen (US Navy, 2008). The presence of the agent on the ship was classified, resulting in physicians incorrectly treating many of the victims (Tucker, 2006).

POST–WORLD WAR II

By the conclusion of World War II, both the Allies and Germany had stockpiled large amounts of chemical agents (Tucker, 2006). The Allied forces divided up the stockpiles of agents discovered in German facilities. Following the end of the war, many of the Allied countries continued to conduct research on the German nerve agents. The rise of the Soviet Union as a power and adversary prompted the United States and other countries to continually search for novel chemical and biological warfare agents (Tucker, 2006). The research and resources that were allotted for these efforts were not trivial, even though they were often overshadowed by the research and development of thermonuclear weapons (Hersh, 1968; Goebel, 2008).

The post–World War II era ushered in the nuclear age. Some felt the age of chemical warfare was over (Smart, 1997), but subsequent events would prove this to be a hasty conclusion. In the United States, research on the G-series agents and medical countermeasures against these agents was accomplished by the late 1940s. Research and intelligence gathering was further hastened by the impressive gains that the Soviet Union made in chemical warfare capability in the years after World War II. By the early 1950s, production of sarin had been initiated in the United States (Smart, 1997). At nearly the same time, Ranajit Ghosh, a chemist at the British company Imperial Chemical Industries plant, developed a new organophosphate compound to use as a potential insecticide (Tucker, 2006). Like with Gerhard Schrader, this compound was deemed too toxic to be used in the field as a pesticide. The compound was sent to researchers in Porton Down, England, synthesized, and developed into the first of a new class of nerve agents, the V agents (Goebel, 2008). Like the G agents, the V agents have a second letter designation: VE, VG, VM, and VX (Coleman, 2005). Of these, VX was the most common. The V series of agents are generally more toxic than the G agents (ATSDR, 2008). In a deal brokered between the British and US governments, the British traded the VX technology for the thermonuclear weapons technology of the United States (Tucker, 2006). The United States produced and stockpiled large quantities of VX after that (Hersh, 1968; Hammond, 1994).

Throughout the 1950s and 1960s, advancements were made in the production and delivery of chemical weapons to include sarin and VX (Smart, 1997). While work on improving masks continued, a renewed concern was the inability to detect nerve agents. Several prototypes were developed in the mid-1950s. Great advancements were made in the therapeutics of agents that inhibited the enzyme acetylcholinesterase (Taylor, 2006; Gupta, 2008; Klaassen, 2008). Atropine was introduced in the early 1950s. Oximes were added as an adjunct to speed up reactivation of the enzyme (Smart, 1997). The autoinjector was developed to overcome user fear of self-injection of atropine. Major advances were made in the use of chemical weapons in artillery (Figure 2.9). For example, the United States developed both short- and long-range rockets filled with chemical agents. But it

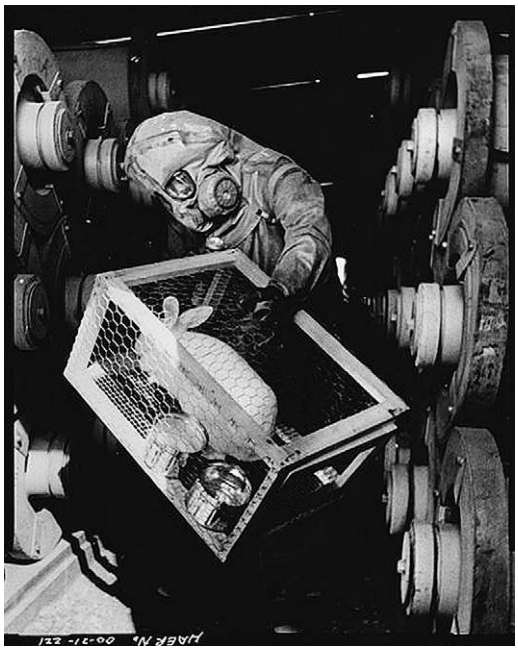

FIGURE 2.9 Testing for leaks at sarin production plant, 1970.

disposed of stockpiles of its chemical weapons in the late 1960s in an operation termed CHASE (which stood for "cut holes and sink 'em") in the sea (Coleman, 2005). In 1969, nerve agent stockpiles were discovered in US depots in Japan after several US military members became ill while doing maintenance (Tucker, 2006). This stockpile, which had been kept secret from the Japanese, created an uproar that later resulted in the disposal of the agents in the Johnston Atoll in the Pacific Ocean.

Defensive equipment, such as improved field alarms and drinking tubes for gas masks, were introduced in the 1960s (Smart, 1997). Great strides were also made in collective protection during the 1960s and 1970s. Although not used extensively since World War I, chemical agents have nonetheless been used for military purposes. The Egyptians allegedly used mustard and possibly nerve agents in the North Yeman civil war in the 1960s (Joy, 1997; Smart, 1997). This was the first reported use of nerve agents in armed conflict. There were allegations that chemical agents were used by the Vietnamese in Laos and Kampuchea in the late 1970s (Coleman, 2005). In the Vietnam War, the United States used defoliants and tear gas, and the Soviet Union was accused of using chemical agents in their war in Afghanistan (Joy, 1997).

INCAPACITANTS AND TOXINS

Incapacitating agents have long been considered an intermediate between chemical and traditional warfare. The Germans investigated the military use of lacrimators in the 1880s followed shortly thereafter by the French (Smart, 1997). The English and French considered using lacrimators in World War I (Smart, 1997). Japanese forces used tear gas against the Chinese in the late 1930s. The US Army used riot control agents and defoliants in the Vietnam War (Smart, 1997). The defoliant known as *Agent Orange* was later potentially linked to several forms of cancer (Stone, 2007). During the 1950s and 1960s, the United States had an active incapacitant program (Smart, 1997). These agents were thought of as more humane than traditional chemical agents because the intent was not to kill. These agents were designated *K agents* and included tetrahydrocannabinol and lysergic acid (Smart, 1997). One of the most extensively studied incapacitating agents was 3-quinuclidinyl benzilate, designated *BZ* by the US Army (Ketchum, 2006). Like many incapacitating agents, BZ was not adopted due to difficulty producing reproducible effects, unwanted side effects, latency in its effects, and difficulty in producing a dissemination that was free of smoke (Smart, 1997; Ketchum, 2006).

There have been multiple attempts to use the toxins from plants and living organisms to develop viable weapon systems. Two that are noteworthy are ricin and botulinum toxin. Ricin, a very potent toxin derived from the castor bean plant, has been recognized as a potential biological weapon since World War I. While the British were developing the V agents, US military researchers patented a procedure for purifying ricin (Harris and Paxman, 2002). The development of a method of disseminating ricin as a chemical weapon proved problematic, which made its use very limited. In 2003, ricin was detected on an envelope processed in a postal facility in Greenville, South Carolina. Postal workers did not develop symptoms of ricin exposure, and the individual who mailed the letter remains at large (Shea, 2004). The development and use of botulinum neurotoxin as a biological weapon was initiated at least 60 years ago (Smart, 1997; Arnon et al., 2001). In the 1930s, during Japan's occupation of Manchuria, the Japanese biological warfare group Unit 731 purportedly fed cultures of *Clostridium botulinum* to prisoners, killing them. The US Army biological weapons program produced botulinum neurotoxin during World War II in response to Germany's biological weapons program (Coleman, 2005). In fact, more than 100 million toxoid vaccine doses were prepared in time for the D-Day invasion of Normandy (Arnon et al., 2001).

RECENT EXPERIENCE

The 1980s proved to be a very significant time for the employment of chemical weapons on the battlefield. In 1980, Iraq invaded Iran (Smart, 1997). The Iraqi armed forces, advised by the Soviet Union, possessed chemical agents and were trained in their use. The war was

FIGURE 2.10 Aftermath of Iraqi chemical weapon attack (1980s).

unequivocally barbarous, and neither side gained an advantage. In many ways, this war had similarities to World War I. By 1983, Iran formally protested to the United Nations (UN) about the Iraqi use of chemical agents. The general consensus was that Iraq used mustard agents and possibly tabun in this war (Figure 2.10). It is estimated that 5% of Iranian casualties, totaling approximately 45,000, can be attributed to chemical agents; the Iraqi Army used chemical agents against the Kurdish minority in northern Iraq as well; and Libya was suspected of using chemical agents when it invaded Chad in 1986 (Smart, 1997).

The late 1980s also saw improvements in defensive equipment, such as the M40 gas mask developed by the United States (Smart, 1997). Other advancements were made in collective protection, decontamination, and detection. In 1984, US president Ronald Reagan issued a statement calling for an international ban on chemical weapons (Tucker, 2006). Subsequently, on June 1, 1990, President George H.W. Bush and Soviet leader Mikhail Gorbachev signed a treaty banning the production of chemical weapons and initiated the destruction of the stockpiles of both nations (Tucker, 2006). In 1993, the Chemical Weapons Convention was convened and signed, and it was implemented in 1997 (Hammond, 1994). As of 2008, the vast majority of UN member states had joined the Chemical Weapons Convention (OPCW, 2008).

In 1990, the Iraqi Army invaded neighboring Kuwait. Subsequently, the United States, at the request of Saudi Arabia, led a coalition to send forces to the area (Smart, 1997). These forces were the largest to operate in a potential chemical environment since World War I. They were provided with atropine autoinjectors, an acetylcholinesterase reactivator, and a nerve agent pretreatment (pyridostigmine bromide). Fortunately, chemical weapons apparently were not used in this conflict, although multiple false alarms were reported. The failure of the Iraqi military to use chemical weapons could be attributed to fear of retaliation, breakdown of communication, changing wind patterns, the surprising speed of the coalition attack, or the fact that Iraqi chemical infrastructure was attacked during the initial portion of the conflict. Since the conflict ended, many coalition veterans have reported a myriad of symptoms that have been commonly referred to as *Gulf War syndrome.* The etiology of this syndrome is unclear despite multiple epidemiological studies (Coleman, 2005). The most recent example of chemical weapons use is the ongoing Syrian civil war (Pellerin, 2013).

TERRORIST USE

One of the reasons why chemical weapons have been used relatively infrequently in combat over the past century is the fear of retaliation by opposing countries. In less organized asymmetrical conflicts, this fear is not as dangerous. At the same time, the potential exploitation of chemical weapons by terrorists is of great worldwide concern. The appeal of these weapons to terrorists lies largely in the fact that many of these chemical agents are cheap and relatively easy to produce, transport, and release. These characteristics, along with the fear associated with the idea of a chemical attack, make chemicals an ideal weapon for terror attacks (Romano and King, 2001). In 1974, Muharem Kurbegovic attacked several public buildings with firebombs in California and claimed to have developed sarin and some other nerve agents (Tucker, 2006). The search of his home resulted in the discovery of various precursor materials for chemical agents and a large amount of sodium cyanide. In 1994, the Aum Shinrikyo, a Japanese religious cult, carried out several attacks both in the subway and in residential areas using sarin produced by the cult's members (Tucker, 2006). A total of 19 people were killed, and over 6,000 received medical attention. Some of those who sought medical attention may have done so due to a fear of exposure. Psychological stress is a common aftermath of a chemical or biological attack (Romano and King, 2001). In the twenty-first century, chemicals that once had been used exclusively by the military have reemerged as contemporary threats. In the fall of 2006, Al Qaeda and associated groups used chlorine combined with traditional car and truck bombings to spread panic in Iraq (Garamone, 2007). These attacks were followed by similar incidents in the subsequent months.

CONCLUDING REMARKS AND FUTURE RESEARCH

So long as there are legitimate uses for chemicals in our society, the risk of chemical agents in conflict and

terrorist activity will always be present. Research continues across the globe for better detection, protection, and treatment of chemical agents. While many countries have denounced and indeed are signatories to various treaties to limit the use and production of chemical warfare agents, nonstate and terror organizations are under no such restrictions. Luckily, chemical weapon use has been limited in both warfare and less formal conflicts. As we progress into the twenty-first century, the use of established chemical warfare agents is a real possibility. The potential use of legitimate industrial chemicals (e.g., the Iraqi burning of petroleum fields in the first Gulf War) and the potential synthesis of new agents should also be recognized. History has demonstrated that chemicals have been used in both organized and asymmetrical conflicts, and preparations for defense and therapy for such encounters is prudent. Chemicals represent a unique force multiplier that simply cannot be ignored in the twenty-first century.

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CHAPTER

3

Global Impact of Chemical Warfare Agents Used Before and After 1945

Jiri Bajgar, Josef Fusek, Jiri Kassa, Kamil Kuca and Daniel Jun

INTRODUCTION

The threat of chemical weapons (CWs), used either by States or Parties to the Chemical Weapons Convention (CWC; Convention on the Prohibition of the Development, Production, Stockpiling, and Use of Chemical Weapons and on their Destruction) or by terrorists, has never attracted so much public attention as it has in the past 10 years. Despite the existing legal documents dealing with prohibition of CWs, for example, Geneva Protocol 1925 and CWC, some incidents of the use of CWs in different conflicts and terroristic attacks have been observed. Moreover, alleged use of CWs was noted during the period from 1925 to the present. It must be emphasized that the theoretical and practical basis for production, storage, and use of CWs still exists. Also, it must be clearly stated that CWs are applicable at any time, in any place, and in large quantities.

CWs consist of chemical warfare agents (CWAs) and the means to deliver to the target. They are characterized by high effectiveness for use against large targets and are known as area weapons or silent weapons. They are relatively low-cost and it is possible to achieve destruction of everything that is living while avoiding destruction of materials and buildings. They are also called the nuclear weapons of poor countries—"poor man's nuclear weapon." It should be pointed out that the use of CWs is connected with the use or release of toxic chemicals; thus, chemical warfare can be considered part of generally observed situations in which toxic chemicals are used or released and influence the environment and humankind.

A number of causal reasons for these events exist but, apart from accidents connected with the release of toxic chemicals from a natural source (e.g., volcanoes), the factors shown in Figure 3.1 or their combinations can be involved.

For military purposes a number of chemicals were tested, but only a few are contained in military arsenals. However, according to the definition in the CWC, any toxic chemical intended for military use must be considered a CW; in other words, the aim is to limit the designation of the compound in question for use as a CW. However, it is possible for terrorists to choose any chemicals with high toxicity.

BACKGROUND

The use of toxic chemicals against humankind is as old as any warfare conflict. The use of the poisoned arrow against humans—not animals—can be considered as the beginning of chemical warfare and is characterized as the intentional use of chemicals.

At the very beginning, chemical warfare was more closely connected with fire. "Greek fire" was an excellent naval weapon because it would float on water and set fire to the wooden ships. There are other examples from history; for example, toxic smoke was used in China in 2000 BC. In Thucydides' *History of the Peloponnesian War* (the fifth century BC war between Athens and Sparta), we find the first description of chemical warfare—the formation of toxic sulfur oxide by burning sulfur. In the year 184 BC, Hannibal of Carthage used baskets with poisonous snakes against his enemy. Both Socrates and Hamlet's father were poisoned with koniin. Aqua Toffana containing arsenic was also a known poison in ancient Italy. Leonardo da Vinci proposed a powder of arsenic sulfide in the fifteenth century. There are many more examples of the use of CWAs (Bajgar et al., 2007b).

Handbook of Toxicology of Chemical Warfare Agents.
DOI: http://dx.doi.org/10.1016/B978-0-12-800159-2.00003-8

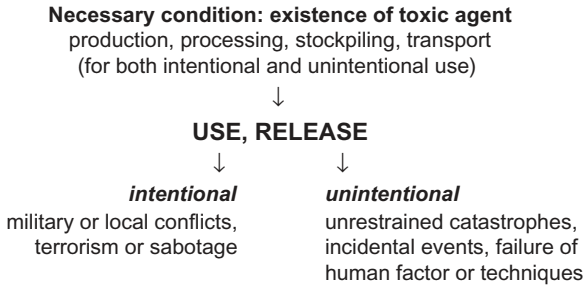

FIGURE 3.1 Possible reasons for release/use of toxic chemicals.

Modern history shows us that terrorists have used other chemicals, such as ricin (Bulgarian G. Markov was poisoned in 1978) or dioxin (the President of Ukraine Viktor Andriyovych Yushchenko was poisoned in 2004).

In a region of Bohemia, a "form" of CW was used as early as 600 years ago. It was in 1422 when the castle of Karlstein, the property of King Charles IV, was besieged and 1822 kegs containing the cesspools of the streets of Prague were hurled into the castle. Allegedly, the stench in the castle was unbearable. According to historical sources, the castle defenders were probably intoxicated with hydrogen sulfide released from the contents of the cesspools and therefore showed typical symptoms of poisoning (Bajgar, 2006).

There were some attempts to prohibit CWs by international agreement or law. Most of the early attempts were bilateral or unilateral agreements directed at the use of poisons. These included the 1675 agreement between France and Germany, signed in Strasbourg, to ban the use of poison bullets.

The first international attempt to control chemical and biological weapons took place in Brussels in 1874, when the International Declaration was signed and included a prohibition against poison and poisoned arms. Despite the first and second Brussels and Hague Conventions (1899 and 1907 signatories agreed not to use projectiles that could spread asphyxiating or deleterious gases), the world witnessed the application of chemicals during warfare to an unprecedented extent during World War I (WWI). A brief summarization of the events connected with the use/release of toxic chemicals is given in Table 3.1.

MILITARY USE OF CWS

The intentional use of CWs for military purposes can be found in both global and local conflicts. A typical example is the warning "Gas! Gas!" This was common in WWI and it is well-known from the E.M. Remarque novel *All Quiet on the Western Front* in which Remarque suggestively describes a chemical attack with chlorine.

During WWI, many chemicals were used, including mustard and asphyxiating and irritant agents. Approximately 45 types (27 more or less irritating and 18 lethal) of toxic chemicals were used. During the latter part of 1914, irritants were used by Germany and France; the effect was insubstantial. In late 1914, Nobel Prize winner Fritz Haber of the Kaiser Wilhelm Physical Institute in Berlin (chemical synthesis of ammonium in 1918) came up with the idea of creating chlorine, although this idea of using toxic chemicals in war was expressed by Admiral Dundonald as early as 1855. Chemical warfare really began in 1915, when German troops launched the first large-scale poison gas attack at Ypres, Belgium, on April 22, using 6000 cylinders to release 168 tons of chlorine gas, killing 5000 British, French, and Canadian soldiers. The date is recognized as "the birthday of modern chemical warfare," and thereafter the belligerent parties frequently used chemical gases against each other. Phosgene was introduced by Germany in late 1915. Soon after the first chlorine attack, the Allies used primitive emergency protective masks. In May 1916, the Germans started using diphosgene, while the French tried hydrogen cyanide 2 months later and cyanogen chloride the same year. The first time mustard gas was used by German troops was July 12, 1917. After its use near Ypres, it was also called yperit.

By the end of the WWI, approximately 124,200 tons of CWAs (chlorine, phosgene, mustard, etc.) had been released, causing at least 1.3 million casualties, of which more than 90,000 were fatal. The threat of the use of CWAs led to the development of protective means not only for humans but also for horses and dogs. The effectiveness of CWs in comparison with classic munition was evident: 1 ton of classic explosives caused 4.9 casualties; 1 ton of chemical munition caused 11.5 casualties; and 1 ton of yperite caused 36.4 casualties (Bajgar, 2006).

THE PERIOD BETWEEN WORLD WAR I AND WORLD WAR II

The terrible casualties of CWs used during WWI and the dangerous consequences for humans and the environment led to the signing of the "Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous and other Gases and Bacteriological Methods of Warfare" on June 17, 1925. This is recognized as one of the unique and famous international treaties on the prohibition of CWs. However, it neither comprises provisions for effective verification nor prohibits development, stockpiling, and transfer of CWs. Moreover, no definition of CWs was included. Despite the provisions of the Geneva Protocol, during 1935 to 1936 Italian troops used CWs during their invasion of Abyssinia (Ethiopia). This first major use of CWs after WWI came

TABLE 3.1 Some Milestones Related to the Use/Release of CWs and Toxic Chemicals

Year(s)	Event
2000 BC	Toxic smoke in China inducing sleep
Fourth century BC	Spartacus—toxic smoke
184 BC	Hannibal—baskets with poison snakes
1168	Fustat (Cairo) —use of "Greek fire"
1422	Bohemia region—cesspools (H_2S)
1456	Belgrade—rats with arsenic
Nineteenth century	Admiral Dundonald—proposed the use of chemicals in war
1914–1918	WWI—start of chemical war
1918–1939	Development of new CWs and protective means
June 17, 1925	Geneva Protocol
December 23, 1936	Lange and Kruger—synthesis of tabun
1940–1945	Concentration camps—cyanide
1943	Synthesis of sarin
1943	Hoffmann and Stoll—synthesis of LSD-25
1945	Kuhn—synthesis of soman
1950	V agents are begun
1961–1968	Production of VX
1961–1971	Vietnam War—herbicides (impurity dioxin)
1962	BZ was introduced into military arsenals
1970	Bicyclic phosphates considered as potential CWAs
1976	Seveso—release of dioxin
1980	Some rumors on intermediate volatility agent
1984	Bhopal incident—release of methylisocyanate
1985	Decision on production of binary CWs
1986, 1987	Demonstration of USA CWs (Tooele) and Soviet Union CWs (Shikhany) to the CD in Geneva
1987	Production of binary CWs
1988	Halabja—use of mustard
1980–1990	Rumors of new nerve agent Novichok
1989	Conference on chemical disarmament, Paris
1991	Persian Gulf War—veteran's syndrome
1992	BZ military stocks of the USA were destroyed
1992	Finalization of the rolling text of the CWC at the CD—Geneva
1993	Signing CWC in Paris
1993	Preparatory Commission on OPCW
1994	CWs of Iraq were destroyed
1994	Aum Shinrikyo—sarin attack in Matsumoto
1995	Aum Shinrikyo—sarin attack in Tokyo
April 29, 1997	CWC—entry into force; establishment of OPCW in The Hague
2000	Research on nonlethal weapons intensified
2002	Moscow theater—Fentanyl derivatives used against terrorists
April 29, 2012	CWs of the State Parties to the CWC will be destroyed but it was prolonged; this period varies from 2015 to 2023 years.
August 2013	Syria—use of sarin

after October 3, 1935, when Mussolini launched an invasion of this country. Despite the Geneva Protocol (Italy had ratified in 1928), the Italians used mustard gas with horrible effects. Later, CWs were used between Japan and China during 1937 to 1945. The Japanese attacked Chinese troops with mustard gas and lewisite. The Japanese, in addition to their biological program, had an extensive CWs program and were producing agent and munitions in large quantities by the late 1930s.

WORLD WAR II

Despite the storing and stockpiling of CWs by the great powers engaged in World War II (WWII), these fatal weapons were not practically used (except small examples) during WWII (probably because of the fear of massive retaliatory use of CWs). An example of intentional use, but not during military conflict, was the killing of prisoners in concentration camps in Nazi Germany. The agent first used in the camps was carbon monoxide, followed by the more "effective" hydrogen cyanide released from Zyklon B. Some experiments with aconitine-impregnated shells and some other toxic compounds including biological agents were tested on prisoners.

However, during WWII, an important step in the preparation of the most dangerous CWA was observed in Germany. In Schrader's group, organophosphates (OPs) were synthesized, primarily with the aim of obtaining more effective insecticides. Between 1934 and 1944, Schrader's team synthesized approximately 2,000 OPs, including two well-known OP compounds, parathion and paraoxon. As early as 1935, the government of Nazi Germany insisted that Schrader switch the primary aim from OP insecticides to CWAs. At present, OPs are widely used in agriculture, medicine (human and veterinary), and industry. These compounds also include nerve agents (the most toxic compounds of the OP group). Nerve agents such as sarin, tabun, soman, and VX are the main compounds of CWAs. The Germans were also the greatest producers of nitrogen mustard and produced approximately 2,000 tons of HN-3.

This part of history is well-known (Koelle, 1963, 1981; Bajgar, 2006; Tuorinsky, 2008; Klement et al., 2013). First synthesis of OP was described in the second half of the eighteenth century. For a long time the first OP (its toxicity was described later) was considered to be TEPP, which was synthesized by Clermont (1854–1855). Philippe de Clermont was a well-known chemist in Sorbonna. Charles Adolph Wurtz dedicated his work to the synthesis of esters of pyrophosphoric acid. These data were specified by Petroianu (2008), and thus he contributed to the discovery that the first synthesis of this OP—TEPP—was performed by Vladimir Moshnin of Moscau. These data are depicted in the work of Patočka (2010). New trends in the synthesis of nerve agents have been described by Halamek and Kobliha (2011).

Tabun was synthesized in 1936, followed by others (sarin at the end of WWII, followed by soman), and production of these agents for the military in large quantities and their stockpiling were recognized after WWII in Dyhernfurth, Poland (e.g., stocks of tabun and some quantities of sarin). The technology was subsequently transferred to Russia, and research and development of new OP nerve agents was continued. During this period, British and American scientists were evaluating the toxic properties of DFP.

THE PERIOD AFTER WORLD WAR II AND THE COLD WAR

At the end of WWII, many Allied nations seized the CWs. Most of the CW manufacturing plants in Germany were taken over and moved to new sites in Russia, such as the military area of Shikhany. This "takeover" prompted other states to begin even more research of CWs. Despite the Allies' own research into CWs, very important technologies and "know-how" were obtained from Nazi Germany for both the United States and the former Soviet Union.

The interest in CW technology was probably one reason for the change of the future border: according to Churchill's history of WWII, the proposed future boundary between Poland and Germany had been primarily agreed to consist, in part, of the Oder River flowing to the Baltic Sea, and its tributary, the Neisse River. Before their confluence, the Neisse consisted of two branches, the East Neisse and the West Neisse. The East Neisse should be the boundary, resulting in slightly more territory for Germany. Stalin held for the West Neisse and progress was delayed. No one knows why Stalin was so insistent in this matter. The reason was probably very simple: the small town of Dyhernfurth (now Brzeg Dolny), a few kilometers north of Breslau (Wroclaw) in the disputed territory, contained a factory for the production of nerve agents. It was estimated that when Dyhernfurth was captured it contained stockpiles of 12,000 tons of tabun, 600 tons of sarin, and an unknown amount of soman. Presumably, the factory was dismantled and, along with their stockpiles, transported to the Soviet Union (Koelle, 1981). It has been documented that the Soviets were ready to conduct a chemical attack and their research and development of CWs were intensified.

In the United States during the 1950s, the chemical corporations concentrated on the weaponization of sarin. At the same time, they became interested in developing CWs that incapacitated rather than killed the targets. Mescaline and its derivatives were studied

but without practical output. Five years later, the new project "Psychochemical Agents" (later K-agents) was established. The objective was to develop a nonlethal but potent incapacitant. Nonmilitary drugs like LSD-25 and tetrahydrocannabinol were also examined. None of these agents was found to be of military importance. The first and only incapacitant was BZ, developed in 1962; however, its stocks were destroyed in 1992, as declared by the US delegation to the Conference on Disarmament in Geneva (Document of CD, 1991). These agents, intended not to kill but to induce incapacity, are covered under the class of nonlethal weapons (Hess et al., 2005).

In the former Soviet Union as a whole during 1940–1945, approximately 110,000 tons of first-generation toxic chemicals were produced, and most of them were yperite, lewisite, and irritating agents. Second-generation CWs were composed of nerve agents such as sarin, soman, V agents, and, to a lesser degree, tabun. The development of new third-generation CWs comprised traditional and nontraditional CWs, for example, blister and irritant agents and nerve gases, including new types such as Novichok 5, whose exact chemical structure is unknown, although some assessments have been made (Bajgar, 2006). It could be a nerve agent having high toxicity, and its effects are difficult to treat using common antidotes.

An example of the unintentional use of CWs has also been observed. In March 1968, thousands of dead sheep were discovered in the Skull Valley area in Arizona in the United States. This area was adjacent to the US Army's Dugway open-air testing site for CWs. Nerve gas had drifted out of the test area during aerial spraying and killed the sheep. One year later, on July 8, 1969, the Army announced that 23 US soldiers and one civilian had been exposed to sarin in Okinawa during the clearing of sarin-filled bombs (Sidell and Franz, 1997).

There are a number of examples of localized conflicts during which CWs have been intentionally used but cannot be verified: from 1951 to 1952 during the Korean War; in 1963, the Egyptians used mustard bombs against Yemeni royalists in the Arabian peninsula; during the Indo-China War (see Vietnam War); in 1970, in Angola, antiplant agents were almost certainly used; and in former Yugoslavia, there were rumors of the use of psychotomimetic agents.

Iraq–Iran and Afghanistan War

On September 22, 1980, Iraq launched its invasion against Iran. There has been mention of the large-scale use of CWAs in the Iran–Iraq war. In November 1983, Iran informed the United Nations that Iraq was using CWs against Iranian troops. Soon after, the use of CWs was unleashed. In addition, mustard and tabun were used. It is well-known that the Iraqi Government used these agents against its own citizens, more conspicuously at Halabja in March 1988. The CWs attack was the largest against a civilian population in modern times. More than 100,000 Iranians were poisoned with CWAs; sulfur mustard was the most frequently used and has induced a number of delayed complications in Iranian veterans (pulmonary, dermal, ocular, immune system depression, reproduction, malignancy, etc.) (Afshari and Balali-Mood, 2006). Other localized conflicts involving alleged use of CWs are described in detail in an extensive review (Robinson, 1971).

The Soviet Union probably used mustard (and nerve gas) in Afghanistan. The Afghanistan war was considered the Soviet Union's "Vietnam." The use of CWs was described by Sidell and Franz (1997). The use of CWs by Soviet forces was also significant and has been confirmed against unprotected subjects. Despite the use of CWs, the withdrawal of Soviet troops from Afghanistan was realized at the beginning of 1989.

Vietnam War

After WWII, the main use of CWs was recorded during 1961 to 1972, when the US Army used defoliants. The herbicide Agent Orange was used during the Vietnam War and led to the injury of more than one million Vietnamese and Americans. Agent Orange (a mixture of 2,4-dichlorophenoxy acetic acid and 2,4,5-trichlorophenoxy acetic acid) contained the chemical contaminant dioxin as an impurity that caused many deaths on both sides. There were other herbicide mixtures such as Agent White (2,4-D and picloram) and Agent Blue (cacodylic acid). The biological effects of dioxin were described by Sofronov et al. (2001). The first major operation of this type was conducted over the Ca Mau peninsula during September–October 1962. The areas sprayed with defoliants were five-times larger and 10-times larger in 1965 and 1967, respectively. The scale of the use of defoliants was approximately in proportion to the overall involvement of US troops. In 1970, herbicides and defoliants were used in tens of tons, especially 2,4,5-T. The area sprayed enlarged from 23 km^2 in 1962 to 22,336 km^2 in 1969. The area exposed to spraying was assessed to be 58,000 km^2 and the number of people exposed was assessed to be more than one million; there were more than 1000 deaths. In addition to defoliants used to destroy vegetation concealing the North Vietnamese, the United States used tear gas for clearing tunnels and bunkers. The irritants CS, CN, and DM were reported to be used. The total CS procured was approximately 7,000 tons from 1963 to 1969.

Development of VX Agent

VX was synthesized in the 1960s on the basis of the results of Tammelin and Aquilonius (Tammelin, 1957;

Aquilonius et al., 1964). The manufacturing of VX began in the United States in 1961. Construction of the United States' VX agent production plant at Newport, Indiana, was completed in 1961, when the first agent was produced. The production facility only operated for 7 years and was placed on standby in 1968 (Smart, 1997).

During the same period, Soviet scientists developed the so-called Russian VX (VR, RVX, R 033) (Kassa et al., 2006; Kuca et al., 2006). The chemical structure of VX was unknown for a long time. Therefore, some attempts to resolve this question have been made (Bajgar, 1968). Because of these ambiguities and difficulties in synthesis, model V agent [EDMM, *O*-ethyl *S*-(2-dimethylaminoethyl) methylphosphonothioate] was initially used in the Eastern Block to study antidotal treatment. Another structural analog of VX known as Chinese VX (CVX) was also developed and studied (Eckert et al., 2006).

A very important step in the development in CWs has been the production of "binary munitions," in which the final stage of synthesis of the agent from precursors is performed in the munition (bomb, shell, or warhead) immediately before or during delivery to the target. In the 1950s, armed forces had begun looking at binary weapons. Until this time, CWs were unitary—the toxic agent was filled in the munition and then stored ready to be used. The binary concept—mixing or storing two less toxic chemicals and creating the nerve agent within the weapon—was safer during storage. The production of binary projectiles began on December 16, 1987, at the Pine Bluff Arsenal in Arkansas.

PERSIAN GULF WAR

On August 2, 1990, Saddam Hussein sent Iraqi troops into Kuwait, allegedly in support of Kuwaiti revolutionaries who had overthrown the emirate. Iraq was known to have a large stockpile of CWs during its conflict with Iran and confirmed that they would use CWs.

President George H.W. Bush ordered US forces to be sent to Saudi Arabia at the request of the Saudi Government (Operation Desert Shield); this was the build-up phase of the Persian Gulf War. As a consequence, in 1996, almost 60,000 veterans of the Persian Gulf War claimed certain medical problems related to their war activities. Some were caused by exposure to nerve agents (released after the bombing and destruction of the sarin production facility). Unexplained "Gulf War Syndrome" with low-dose exposure to CWAs was suggested as a possible cause. Extensive research failed to find any single case of the problem. However, some health effects, including alterations to the immune system 3 months after the exposure to low concentrations of sarin, were demonstrated (Kassa et al., 2001, 2003). In the desert, during the autumn and winter of 1990–1991, the threat of chemical warfare became very real to allied military personnel. It was demonstrated by the UN Commission that major Iraqi agents were mustard, tabun, sarin, and cyclosarin. Mustard agent was relatively pure, but nerve agents were a complex mixture of the agent and degradation products. During the period from June 1992 to June 1994, the Commission's Chemical Destruction Group destroyed 30 tons of tabun, 70 tons of sarin, and 600 tons of mustard, which were stored in bulk and in munitions.

Suddenly, it became clear to the whole world that there were countries with CWs and biological weapons, and there were other countries that might obtain or produce them.

SYRIA

The conflict in Syria has been the last conflict in which the use of CWs was confirmed by the UN Mission (UN, 2013). Nerve agent sarin was used in an attack on the Ghouta area of Damascus (August 21, 2013). It is not the intention of this chapter to evaluate political situations; however, it was not possible to decide exactly who used sarin (current government or FSA) against civilian victims. First complex reactions were published in October 2013 in the CBRNe World (Higgins, 2013; Johnson, 2013; Kaszeta, 2013; Winfield, 2013). For the Mission, there were not ideal conditions: difficult political situation, chaotic scene, and timing that was not ideal. However, the report was well-structured and conclusions were clear: sarin was present in some samples and rocket remains, and selected survivors showed symptoms supporting sarin exposure (Johnson, 2013).

There are different data regarding the number of victims, initially varying from hundreds to thousands. The Syrian Observatory for Human Rights reported more than 500 deaths and thousands of patients displaying "neurotoxic symptoms," including civilian people and children. Medicine Sans Frontiers said at least 3600 patients had these symptoms and, of those patients, 355 had died. UN Mission selected 36 from 80 survivors who met the criteria established by the Mission. Symptoms consistent with organophosphate intoxication were observed: decreased consciousness (78%), dyspnea (61%), blurred vision (42%), eye irritation or inflammation (22%), lacrimation (8%), miosis (14%), salivation (22%), vomiting (22%), and convulsion (19%). Johnson (2013) did not mention the postmortem samples or data regarding dead persons. Treatment of victims and the course of poisoning, including laboratory results, have not been specified. However, laboratory examinations would be useful, as in case of Tokyo victims (Polhuis et al., 1997). It would be possible to use other methods

of laboratory diagnoses of nerve agent intoxication, as described previously (Noort et al., 2009; Schans van der, 2009; Bajgar, 2013). Autopsies of victims were not conducted but would have been useful, as would postmortem examinations of dead animals. Regarding CWs of Syria, they will be destroyed under the supervision of Organization for Prohibition of Chemical Weapons (OPCW) (for Syria, CWC entered into force on October 14, 2013) and with international assistance.

UNINTENTIONAL USE OF TOXIC CHEMICALS

There are two main accidents connected with the release of toxic chemicals. In July 1976, in Seveso, Italy, more than 40,000 people were exposed to dioxin, a persistent and highly toxic chemical. The first signs were skin lesions appearing on children, and after some months there was evidence of chloracne. Health consequences have been observed from that time to the present. The Seveso accident was possibly the most systematically studied dioxin contamination incident. A similar contamination of one building of the Spolana company in Neratovice (a town in the former Czechoslovakia) was also observed (Bajgar et al., 2007a; Pelclová et al., 2011). Another example, the Bhopal accident, is probably the greatest industrial disaster in history. In 1984, on December 2 and 3, water inadvertently entered the methylisocyanate storage tank (containing approximately 40 tons of this chemical). As a result, methylisocyanate was released into the surrounding area. There was no warning. Many people who inhaled high concentrations of toxic gas asphyxiated because of extensive lung damage. Approximately 150,000 people were intoxicated (50,000 seriously poisoned) and more than 2500 people died (Bajgar, 2006).

TERRORIST USE OF CWS

Terrorists have expressed an interest in nerve agents and have deployed them in attacks on unprotected civilians (Rotenberg and Newmark, 2003). A Japanese religious cult, Aum Shinrikyo, independently manufactured numerous chemical and biological agents. The first such attack with sarin occurred in Matsumoto in 1994 and in the Tokyo subway in 1995. Thousands of people were affected and dozens of people died (Ohtomi et al., 1996; Nagao et al., 1997; Okomura et al., 1998; Yokoyama et al., 1998). In Matsumoto (1994), 600 people were poisoned and hospitalized and seven died (Morita et al., 1995; Nakajima et al., 1997; Yoshida, 1994). The attack in the Tokyo subway (1995) resulted in 5500 people seeking hospital evaluation and 12 deaths (Bajgar, 2006). An interesting terroristic act was described by Tsuchihashi et al. (2005)—a fatal intoxication with VX administered percutaneously.

Nerve agents belong to the group of OPs. These compounds in the form of pesticides are commercially available and are used in agriculture, which can lead to professional, suicidal, or accidental intoxication. The mechanism of action, diagnosis, and treatment of intoxication with OP pesticides and nerve agents are very hot topics at present. Moreover, some principles of the effects, diagnosis, and therapy are very similar for OP and highly toxic nerve agents; therefore, the principle of action and effective treatment can be applied in general for the civilian sector, too.

The use of these chemicals was observed in Moscow in 2002. The Moscow theater hostage crisis was the seizure of a crowded theater on October 23, 2002 by approximately 40 armed Chechen militants who claimed allegiance to the separatist movement in Chechnya. They took 850 hostages and demanded the withdrawal of Russians from Chechnya and an end to the Chechnya war. The leader of the terrorists was 22-year-old Movsar Baraev. After 2.5 days of waiting, Russian forces used an unknown gas pumped into the ventilation system. Officially, 39 terrorists and at least 129 of the hostages (nine of them foreigners) were killed. Some estimates have put the civilian death toll at more than 200. It was thought that the security services used an aerosol of a CWA, first assessed as BZ, but later it was specified that an aerosol anesthetic of the Fentanyl type was used (Bajgar and Fusek, 2006).

In the hospitals, the survivors were cut off from any communications with the outside and their relatives were not allowed to visit them. An incorrect list of hospitals for victims was released. The main problem was the lack of information about those dealing with the identification and characterization of the chemical used and the unavailability of known antidotes (e.g., naloxon) by medical staff treating the victims (Bajgar et al., 2007a). It appeared from this event that there were compounds not explicitly enumerated in the CWC and therefore not controlled by this Convention. Fentanyl can be considered as a nonlethal weapon (a group of so-called calmatives) and these chemicals can also be used to incapacitate animals; of course, its use against humans is not excluded (Bajgar, 2006; Hess et al., 2005).

NEGOTIATIONS

Although the Cold War was continuing, the political situation led to increased activities in international negotiations. At the Conference on Disarmament in Geneva, some attempts to negotiate a ban of CWs were begun, first as the ad hoc Working Group, and later as the ad hoc

Committee on Chemical Weapons with the mandate to negotiate the text of a convention banning CWs.

The discussions in Geneva were more intensive from 1987 and, in 1992, the elaboration of the so-called rolling text of future CWCs was finished. During these negotiations, the text of future Conventions ("rolling text") was enlarged: the final report (CD/342) of February 2, 1983 contained 23 pages; the same report of August 23, 1985 (CD/636) had 46 pages; and CD/952 of August 18, 1989 contained 134 pages. Simultaneously with the Geneva negotiations, in September 1989, the Memorandum of Understanding between the Governments of the United States and the USSR regarding a bilateral verification experiment and data exchange related to prohibition of CWs, otherwise known as the Wyoming Meeting, started negotiations between two main possessors of CWs. These countries also contributed to the negotiations in Geneva: they demonstrated their CWs to the Conference on Disarmament in the United States in November 1986 (Tooele) and in the USSR in October 1987 (Shikhany). The final document of the Convention is approximately 200 printed pages. The Convention was then agreed on in New York at the UN General Assembly and signed in Paris in 1993. The CWC (Convention on the Prohibition of the Development, Production, Stockpiling, and Use of Chemical Weapons and on their Destruction) entered into force on April 29, 1997, 180 days after the deposit of the 65th instrument of ratification of the Convention by Hungary. At this time, 87 countries ratified the CWC and became original States Parties to the Convention. Simultaneously, the OPCW in The Hague started its work of supervising the destruction of CW stocks and monitoring the world's chemical industry to prevent future misuse. There are many activities of the OPCW, for example, training of the inspectors for control of destruction of CWs including their medical protection, research, and supported activities, solving problems due to practical implementation of the CWC, control of chemical and military facilities, and other activities. Russia and the United States were unlikely to meet the final stockpile destruction deadline of April 29, 2012. By the middle of 2008, 183 signing States and 194 recognizing States had adhered to the Convention (Davey, 2008). However, there are still States that are nonsignatories to the Convention. CWs have a long and ancient history. A lack of CW use in WWII suggested that "gas warfare" had ended. However, further development and the utility of chemicals in Vietnam and in terrorist attacks have maintained a military interest in CWs.

Current information of OPCW provides the status of the destruction of CWs. April 29, 2012 was suggested to be the prolonged period for CW destruction. Seven State Parties declared they possessed CWs (Albania, India, Iraq, South Korea, Libya, Russia, and the United States). The stocks of Albania, India, and South Korea were destroyed. Until this date, 73.72% of all declared CWs (the sum of 71,195.086 tons) were destroyed (Streda, 2013). On the basis of the Conference of the State Parties (16th Session, December 2011), the destruction period was prolonged for Russia (2015), Libya (2016), and the United States (2023). Simultaneously, CW-producing facilities were also destroyed or dismantled—13 State Parties declared 70 of these facilities (Bosnya and Hercegovina, China, France, India, Iraq, Iran, Japan, South Korea, Libya, Russia, Serbia, Great Britain, and the United States) and 43 of these objects were destroyed and 21 were dismantled for peaceful purposes.

It is clear that the use (incidental or otherwise) of toxic chemicals has impacts on different spheres of human existence, such as state structures and infrastructure, economics, psychic and public behavior, and the environment. Toxic chemicals are a great consumer of natural sources, both renewable and nonrenewable. They also consume raw materials and energy and, as a consequence, cause pollution of the environment and lead to deficiency of raw materials throughout the world and therefore an unequal distribution of the world's natural sources. The impact on the psychology of humankind is also important, following either chemical wars (both global and local) or use of these chemicals by terrorists. The development of new technologies is equally important because they influence, positively and negatively, further human development. Research in this direction not only can contribute to "improvement" of chemicals to obtain more effective CWAs but also can improve our knowledge of basic sciences (toxicology, neuropharmacology, etc.) and allow us to better understand physiological functions in general. It is appropriate to recall the history of cholinesterases and their inhibitors. The existence of cholinesterases was predicted by H.H. Dale in 1914, 14 years before acetylcholine was demonstrated as a natural constituent of animal tissues. This research approach was changed during WWII and cholinesterases acquired a special significance in the context of chemical warfare and nerve agents (Silver, 1974). Another publication in this area (Koelle, 1963) can be considered as the first to deal with anticholinesterase agents including CWAs—nerve agents. One can only hope that in the future the only physiological and pharmacological research will be performed in a nonmilitary framework, but that may not be the case.

CONCLUDING REMARKS AND FUTURE DIRECTION

The threat of the use (either military or terroristic) of CWAs (and other toxic chemicals) still exists. The military use of these agents is limited, but their terroristic use is unlimited. The spectrum of these agents is very large and the ability to be prepared against the use of toxic chemicals is necessary.

Acknowledgment

This work was supported by the grant of Ministry of Defense (Czech Republic): "A long-term organization development plan 1011."

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CHAPTER

4

The Tokyo Subway Sarin Attack: Acute and Delayed Health Effects in Survivors

Tetsu Okumura, Kenji Taki, Kouichiro Suzuki, Takemi Yoshida, Yukio Kuroiwa and Tetsuo Satoh

INTRODUCTION

The Tokyo subway sarin attack occurred in 1995. Prior to the disaster in Tokyo, Matsumoto sarin attack happened on June 27 in 1994 in Matsumoto city, Nagano Prefecture at the center of Japan main land. Sarin was dispersed into the open air using an electric heater fan to direct it to the target apartment. Eventually, eight people died and 660 were injured. In addition to these injured patients, one woman exposed to sarin died after 14 years hospitalization. This was the first terrorist attack using sarin on the general public in the world, an incident which served as a wake-up call for anti–nuclear, biological, and chemical (NBC) terrorism policy throughout the world. In the 10 years since the attack, efforts to combat NBC terrorism have focused on rapid and effective measures to respond to attacks employing nerve agents such as sarin.

SARIN TOXICITY AND MECHANISM OF ONSET

Sarin is an organophosphate compound. Within the context of chemical weapons, organophosphates are collectively referred to as "nerve agents," of which sarin, tabun, soman, and *O*-ethyl *S*-[2-(diisopropylamino) ethyl] methylphosphonothioate (VX) are examples. Organophosphates inhibit the enzyme acetylcholinesterase (AChE), which degrades acetylcholine (ACh), a neurotransmitter substance that acts locally on nerve synapses. Once organophosphates bind to the phosphorylate AChE to inhibit its activity, ACh accumulates at nerve terminals, resulting in enhanced ACh activity at receptor sites. ACh effects can be functionally classified based on their site of action and can have muscarinic, nicotinic, and central nervous system (CNS) effects. These effects cause the major symptoms associated with an acute organophosphate toxicity. Muscarinic effects increase parasympathetic nerve activity and cause miosis, visual disturbances (accommodation disorder), increased salivary and bronchial secretions, bronchospasm, bradycardia, and increased gastrointestinal peristaltic activity (e.g., abdominal pain, nausea, vomiting, and diarrhea). Nicotinic effects, due to hyperstimulation of neuromuscular junctions, cause fasciculations, muscle weakness, and respiratory paralysis, and increased sympathetic nerve activity leads to miosis, sweating, tachycardia, and hypertension. CNS effects due to ACh, when severe, include anxiety, headaches, excitement, ataxia, somnolence, disorientation, coma, and seizures.

Well-known symptoms of sarin toxicity include miosis, hypersecretions, bradycardia, and fasciculations. However, the mechanism of organophosphate toxicity seems to involve conflicting actions. For example, mydriasis or miosis, and bradycardia or tachycardia may occur. Acute respiratory insufficiency is the most important cause of immediate death. Early symptoms include (i) tachypnea due to increased airway secretions and bronchospasm (a muscarinic effect), (ii) peripheral respiratory muscle paralysis (a nicotinic effect), and (iii) inhibition of respiratory centers (a CNS effect), all of which lead to severe respiratory deficiency. If left untreated at this stage, death will result. Cardiovascular symptoms may include hypertension or hypotension. Various arrhythmias can also occur, and caution is required when the QT interval is prolonged. In particular, if hypoxemia is present, fatal arrhythmias may occur with intravenous administration of atropine

Handbook of Toxicology of Chemical Warfare Agents.
DOI: http://dx.doi.org/10.1016/B978-0-12-800159-2.00004-X

sulfate, which means that this drug should be given intramuscularly to victims of sarin poisoning. Common gastrointestinal symptoms of this poisoning include nausea, vomiting, and diarrhea.

An intermediate syndrome lasting 1–4 days after sarin exposure appears to exist (De Bleecker, 1992). This is due to prolonged AChE inhibition, and it is associated with acute respiratory muscle paralysis, motor nerve paralysis, and cervical flexor and proximal muscle paralysis. Recumbent patients who have difficulty raising the head and neck require particular care. However, the intermediate syndrome has not been reported with nerve agent toxicity in animals or humans (Sidell, 1997), although this syndrome is well documented in humans following large exposure to organophosphate and carbamate pesticides (Gupta, 2005; Paul and Mannathukkaran, 2005; Gupta and Milatovic, 2012). The cause of the intermediate syndrome may be toxicity due to massive organophosphate exposure or inadequate treatment of such exposure (intestinal decontamination, antidote administration, and respiratory management). In organophosphate-induced delayed neuropathy (OPIDN), seen 2–3 weeks after exposure and characterized by distal muscle weakness without fasciculation, the pathophysiology is not well understood. OPIDN was first reported in the 1930s due to contamination of Jamaican ginger (nicknamed *Jake*) by organophosphates. This incident (so-called ginger jake paralysis) caused lower limb paralysis in about 20,000 victims. OPIDN symptoms have also recently been reported in Matsumoto and Tokyo subway sarin victims (Sekijima et al., 1997; Himuro et al., 1998). Inhibition and aging of neuropathy target esterase plays a role in OPIDN, but despite several basic research studies, the detailed pathophysiology has not yet been established, making OPIDN difficult to treat.

OVERVIEW OF THE TOKYO SUBWAY SARIN ATTACK

The attack took place during the morning rush hour, at about 8 a.m. on March 20, 1995, the day before the Spring Equinox holiday. The attack was carried out by members of a cult known as Aum Shinrikyo to distract police from carrying out a raid on the group's headquarters. The terrorist target was government buildings in Kasumigaseki in the heart of Tokyo. Most offices in Kasumigaseki open for business at 9:30 a.m., but the early-morning rush hour was unusually heavy because it was a Monday. Some believe that the time of 8 a.m. was chosen because some cult members had inside information about the government offices. Police suspected, based on an undercover investigation that they were conducting, that Aum Shinrikyo was manufacturing sarin for use in a terror attack, but few people, even within the police department, were aware of this fact. The police did not have personal protective equipment (PPE), which meant that they had to borrow PPE and receive training on use of the equipment from the Self-Defense Forces. Members of the Self-Defense Forces were alerted to some of Aum Shinrikyo's planned activities, but the general public, including healthcare providers and fire department personnel, knew nothing of these activities (Figure 4.1).

According to a subsequent police report, the terrorists placed sarin in five subway trains in the following way.

FIGURE 4.1 Scene from a sarin attack at Tsukiji station.

Approximately 600 g of sarin at a concentration of 33% was mixed with hexane and *N*, *N*-diethylaniline and placed in a nylon/polyethylene bag. Five terrorists then wrapped the bags in newspaper, punctured the bags with the tips of their umbrellas, and left the bags on the trains. In this way, the sarin seeped out of the bags and vaporized, but no other active means of dispersal were used. In this sense, as well as the relatively low number of deaths, the Tokyo subway sarin attack was not considered a full-scale attack.

Of the bags of sarin used in the attack, two bags were not punctured. These bags were returned to the police laboratory for analysis. At Kasumigaseki, one of the subway stations on the Chiyoda subway line, two station employees collapsed and died on the platform after they cleaned and removed one of the bags that didn't get punctured, even though they were wearing gloves. The number of victims of this attack varies depending on the source, but all known information confirms that 12 people died in the attack, and it is generally believed that at least 5,500 victims suffered mild to serious injuries. Firefighting agencies estimate 5,642 victims, and the police, 3,796 victims, while official figures released by the subway company put the total number of victims at 5,654. This includes the 12 who died (10 passengers, 2 employees), those hospitalized (960 passengers, 39 employees), and those treated for minor injuries (4,446 passengers, 197 employees).

Thus, the way in which we use the lessons learned from this attack will affect our ability to deal adequately with future terrorist attacks using sarin, which could be even greater and more serious with respect to the number of victims. Can we really assume that only 12 of the approximately 5,500 victims died because the Japanese medical system was particularly well prepared for such an eventuality? Probably not. It is more likely that the relatively small number of fatalities was due to the low concentration of sarin and the passive means of dispersing it. From this perspective, the Matsumoto sarin attack one year earlier was more aggressive than the Tokyo subway sarin attack. In a trial after the Matsumoto incident, it was revealed that a 70% concentration of sarin was actively volatilized using an electric heater and dispersed using an electric fan. A total of 7 victims died and 660 were injured and one victim died 14 years after sarin exposure. In other words, if the Tokyo subway sarin attack had been conducted using the same means as those employed in the Matsumoto sarin attack, the number of fatalities may have been 50 or 60. So humanity has not yet experienced the effects of a full-scale sarin attack in a major city.

Even if it did not rise to the level of a major attack, this incident was the first chemical terrorist attack in a large city. There were few first-responders who could even have conceived of such an attack, let alone be prepared to rapidly evacuate victims from the subway stations. Many passengers who had difficulty walking rushed out of the trains and onto the subway platform and fell down, which would have increased their exposure to the sarin permeating the stations. In addition, the site to which many of the victims were finally evacuated at ground level, where they could lie down, was close to an air exhaust vent from the subway below, so the exposure continued.

The first call for an ambulance came 9 minutes after the 8 a.m. attack, with the first report of a "victim with seizures at Kayabacho Station." By 8:15 a.m., the reports of victims started to increase. Around this time, the fire department received a report from Tsukiji Station stating that "an explosion occurred and several people were injured." Calls for ambulances eventually came from 19 subway stations, and after 8:30 a.m., victims began to pour into local clinics and hospitals. According to the Tokyo Fire Department, 5,493 people were treated at 267 medical institutions in Tokyo, and 17 people were treated at 11 medical institutions outside Tokyo. Among the victims, 53 were seriously injured (Ieki, 1997). Another source states that a total of 6,185 people were treated at 294 medical institutions (Chigusa, 1995). The discrepancy in the number of victims reported by different agencies attests to some of the confusion at the time. St. Luke's Hospital received the largest number of victims (640 on the day of the attack), probably because of its close proximity to the Hibiya line, where a large number of victims were located, and because of a report on television stating that "St. Luke's Hospital has the antidote for treatment."

EMERGENCY TREATMENT OF SARIN TOXICITY

The standard treatment for sarin toxicity includes (i) maintaining the airway, (ii) assisting breathing, and (iii) supporting circulation. In victims of the Tokyo subway sarin attack, endotracheal intubation was performed frequently. However, in the Matsumoto sarin attack, endotracheal intubation was more difficult to do in many victims because of airway hypersecretion and bronchospasm. This difference in symptoms is attributable to the 70% concentration and the active means by which the sarin was dispersed at Matsumoto, as opposed to the much lower 33% concentration and passive means of dispersal employed in Tokyo. Dr. Frederick Sidell, an expert on chemical terrorism in the United States, advocated decontamination, drugs, airway, breathing, and circulation (DDABC) as the basic treatment for nerve agent poisoning. Even if the advised emergency treatment is followed, initial efforts to achieve adequate ventilation may be in vain. Efforts to achieve adequate ventilation should be made after at least initial administration of atropine to control the buildup of airway secretions and bronchoconstriction (Sidell, 1997). If healthcare

professionals learn from the Matsumoto attack, they can better recognize early parasympathetic nervous symptoms, including miosis, hypersecretion, and rhinorrhea, as common indications of chemical terrorism due to nerve agents, and therefore be able to institute appropriate treatment with antidotes in time. In large-scale disasters with many victims, treatment is often deferred in those with cardiopulmonary arrest (CPA; so-called black tag). However, at St. Luke's Hospital, one in three persons with CPA and two patients with respiratory arrest made a full recovery and were discharged. This high rate of recovery and return to the community is unlike that seen in other types of disasters. Therefore, if medical resources are available, all victims of a sarin attack should be aggressively treated, including cardiopulmonary resuscitation (CPR) when necessary.

The global standard for the treatment of sarin toxicity is the administration of (i) atropine, (ii) an oxime agent like 2-PAM, and (iii) diazepam (Medical Letter, 2002).

Recommended doses of atropine are 2 mg in patients with mild symptoms that are primarily ocular, but without respiratory symptoms or seizures; 4 mg in patients with moderate symptoms, including respiratory symptoms such as dyspnea; and 6 mg in patients with severe symptoms, including seizures and respiratory arrest. The standard administration route should be intramuscular. As mentioned previously, intravenous administration of atropine in the treatment of severe symptoms such as hypoxemia can induce ventricular fibrillation; thus, intramuscular administration is advised. Oxime agents such as 2-pralidoxime methiodide (2-PAM), or 2-formyl-1-methylpyridinium iodide oxime should also be given. The recommended dose for 2-PAM in moderate and severe cases of inhalation, or for liquid exposure to a nerve agent, is 1 g by intravenous infusion over 20–30 min. Further continuous administration of 500 mg/h may also be required in severe cases. Since the rate of aging of the nerve agent–enzyme bond is correlated with time until 2-PAM is administered, if the aging half-life of sarin is 5 h, then 2-PAM must be administered before this time. The oxime of choice for sarin and VX is 2-PAM, but asoxime chloride (HI-6) should be used for soman and obidoxime for tabun. Seizures are treated with diazepam. This three-drug combination (atropine, 2-PAM, and diazepam) is the global recommendation for sarin toxicity, and autoinjectors are available in several countries (Vale et al., 2006) (Figure 4.2).

After the Tokyo subway sarin attack, St. Luke's Hospital, which treated 640 victims, used about 700 ampules of 2-PAM and 2,800 ampules of atropine (Okumura et al., 1998). This calculates out to 550 mg of 2-PAM and 2.2 mg of atropine per victim. The route of administration was intravenous in all cases, with a total dose of 1.5–9 mg of atropine in severe cases (Okumura et al., 1996); this range of dose reflects the low concentration and passive means of sarin dispersal used in the Tokyo attack.

However, in Tokyo, no one was saved by administration of 2-PAM; conversely, no one died because they did not receive it. In other words, if the victims' survival was the ultimate goal, there was no clinical evidence that 2-PAM was effective. The only reported finding was a more rapid return of plasma pseudocholinesterase levels to normal in patients who received 2-PAM, as compared to those who did not. But in terms of long-term prognosis, this does not rule out the effectiveness of oxime

FIGURE 4.2 Sarin victims at St. Luke's International Hospital.