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REVIEW

Healthcare Aspects of Chemical and Biological Warfare Agents: Technologies for the Detection, Decontamination, and Treatment

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Abstract

Many biological and chemical warfare (BCW) agents' events have occurred since 2000, such as the chemical bombings of Halabja by Saddam and Turkey's attack on the North and Northeast of Syria in 2019. During the occupation attacks on "Serêkaniyê", in October 2019 by Turkey many people targeted and injured as a result of the use of chemical weapons. We have to mention that advances in new technologies such as genetic engineering, nanotechnology, biotechnology, neurobiology, and artificial intelligence not only contribute to the proliferation of traditional BCW agents, but also motivate the production of new agents. So, the danger of using traditional and new BCW agents by governments and terrorist groups is becoming more serious day by day. Therefore, on the other hand, it is very necessary to improve decontamination methods, identification methods, and treatment of those who have been exposed to these factors.

This study explains BCW types, methods for decontamination, and technologies for detecting BCWs, and finally presents the therapies for BCW-exposed peoples and animals.

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1. Introduction

A chemical warfare agent (CWA) is a highly toxic compound that is often used as part of terror attacks or acts of war. A CWA can be a nerve agent or blistering agent, or it could be a toxin or another chemical attack. There are many ways to be exposed to CWAs, including gas, aerosol, liquid, or gel-like composites of CWA and polymer (usually 5–10 wt% polymer) (Snider et al. 2022).

The use of toxic substances as weapons has been documented throughout human history, spanning thousands of years. Historically, the utilization of toxic substances as weapons has been linked to traditional hunting techniques, such as the application of poisons to arrows or spears, the contamination of water sources (such as watering holes or fishing spots), or the use of toxic fumes to fumigate animals. As a result of the German chlorine attack in Ypres on 22 April 1915, World War I saw a decisive new phase in the history of chemical weapons. There were more than 200,000 tons of chemical warfare agents (CWA) produced by the major powers (Germany, France, Britannia, Russia, and the United States), and the most of these were used through all the methods available at the time (gas cylinders, tube artillery, mortars, hand grenades, and rifle cartridges). Various rapidly acting lethal substances were prioritized (chlorine, phosgene, diphosgene, chloropi-crin, hydrogen cyanide), and vesicants (mustard gas) were also included. Chemical weapons eliminated about one million soldiers from action, and about 10% of them died (Pitschmann 2014).

During World War II, major powers were prepared to use chemical weapons on a large scale, both in terms of technical and organizational readiness. This is evidenced by the fact that they stockpiled over 400,000 tons of chemical warfare agents (CWA), two-thirds of which were vesicants such as mustard and lewisite. However, Germany went further and produced substantial amounts of second-generation chemical weapons, including over 12,000 tons of Tabun and a smaller amount of Sarin, until 1944. A notable aspect of World War II history is the use of carbon monoxide and hydrogen cyanide (Zyklon B) to exterminate Jewish people and other nations in concentration camps, as well as possible chemical-toxicological experiments on humans (Pitschmann 2014).

Qualitative changes occurred in the development of chemical weapons after World War II. During the Cold War, nerve agents and more effective V agents were introduced and mass-produced. New concepts of conducting "non-lethal" warfare using psychoactive substances emerged, particularly hallucinogenic glycolates (BZ). Highly effective irritants were also developed and used in military conflicts, such as the CS agent in the Vietnam War (Pitschmann, 2014). During the Cold War, the United States developed third-generation chemical weapons using binary ammunition with nerve agents such as sarin, VX, and IVA. The Soviet Union responded with an extensive program (code name FOLIANT, NOVICHOK) to develop fourth-generation chemical weapons with even more potent nerve agents. Third World countries acquired chemical weapons as a cheaper alternative to nuclear weapons, with Iraq amassing a large chemical arsenal including over 3,800 tons of toxic chemicals such as mustard gas, tabun, and sarin, with the help of foreign companies (Pitschmann 2014).

The main aims of this review are overview of toxicological, clinical and biochemical researches and properties of several poisonous chemical compounds that are used as BCW helps us to achieve the following goals:

- Providing basic information in the field of basic toxicology
- Providing basic and essential information for the preparation of antidotes.
- Presenting the methodology of detection of BCWs and applied treatment for victims

2. Purpose of CWA application

Chemical and biological weapons have been used for various purposes throughout history. They have been employed as a tool for propaganda and to stigmatize an adversary, with claims of alleged use or development being made by various parties. These weapons also possess the ability to terrorize beyond

their physical effects, as demonstrated by the Tokyo subway sarin attack in 1995. Chemical weapons have been used to harass enemy troops and break the deadlock of trench warfare during World War I. The use of incapacitating agents in counter-terrorism has become a concerning development, with the potential to legitimize the use of certain chemical weapons. Lastly, demoralization has been historically achieved through the use of chemical and biological weapons, with even a small-scale use offering a disproportionate psychological advantage over an adversary.

2.1. Allegations and Propaganda

Biological and Chemical Warfare (BCW) has proven to be a potent weapon in propaganda campaigns. Its alleged use or development has been adroitly employed to stigmatize an adversary and castigate the actions of others as deplorable. The Soviets have made spurious claims, including that the HIV virus originated from CIA-linked laboratories, and that the US-funded WHO Malaria Control research unit in New Delhi was involved in using mosquitoes and yellow fever virus as BW agents. Similarly, during the Korean conflict, the Chinese and North Korean authorities accused the US of exploiting poisonous bugs and other germs (Tucker 2000).

2.2. Terrorising

Chemical and biological weapons possess the ability to evoke terror beyond their demoralizing effects. A clear demonstration of such terrorizing effects is illustrated by the release of sarin in the Tokyo subway in 1995. This attack resulted in 12 fatalities, 54 severely injured individuals, and approximately 980 with mild or moderate symptoms. Nevertheless, more than 5,000 people sought emergency medical assistance, reporting psychosomatic symptoms induced by the fear and uncertainty surrounding the possibility of exposure (Ilchmann 2014).

2.3. Harassing

During World War I, chemical weapons were used to force troops to leave their positions in trenches and break the deadlock of trench warfare. Two types of agents were employed: nonpersistent agents to soften up an enemy position immediately before an assault, and persistent agents to be used against positions that were not to be occupied immediately. Chlorine, phosgene, and mustard gas were responsible for most chemical weapons injuries and deaths during World War I (Ilchmann 2014).

2.4. Incapacitation

The use of incapacitating agents in counter-terrorism has become increasingly unconstrained, with the acquisition, deployment or use of irritant-agent weapons being used for such purposes. The Bradford Non-Lethal Weapons Research Project Report notes that the issue of lethality is a distraction, and agents designed to incapacitate rather than kill have been a common feature of several past offensive chemical and biological weapons programs. The report also highlights the difficulty of delivering a safe and reversible but incapacitating dose to all individuals in a given area, notwithstanding the differences in age, size and health of those individuals and the problems of uneven concentrations and cumulative intake of the agent. An example of the use of toxic chemicals beyond law enforcement is the use by the Russian Federation in 2002, which resulted in 129 deaths among hostages due to the effects of the gas. The use of incapacitating agents is a concerning development, with the potential to legitimize the use of certain chemical weapons in counter-terrorism efforts (Ilchmann 2014).

2.5. Demoralization

Demoralization refers to the use of tactics or weapons to undermine enemy morale and break their will to fight. Chemical and biological weapons (CBW) have been used historically for this purpose. For example, Italian forces used chemical weapons in Ethiopia not necessarily to kill but to demoralize retreating Ethiopian forces. Similar claims have been made over the use of harassing chemicals in China. In the ongoing conflict in Syria, the demoralizing effect of CBW has been suggested as a possible motive for their use. Even a small-scale use of CBW may offer a disproportionate psychological advantage over an

adversary by demoralizing their forces (Ilchmann 2014).

3. Types of Chemical and Biological Warfare Agents and their Mechanism of Action

3.1. Choking agents

3.1.1. Chlorine (Cl_2)

Chlorine gas (Cl_2) is a hazardous substance that is commonly used in various industrial processes, such as chemical manufacturing and water purification. However, exposure to high doses of chlorine gas, which can occur in the event of an accident or a deliberate act, can be lethal and cause severe harm to human health. Unfortunately, chlorine gas has also been used as a chemical weapon in the past, and there have been reports of alleged and proven use in recent armed conflicts. Animal studies have been conducted to investigate the effects of chlorine gas exposure on the respiratory and cardiovascular systems. When chlorine gas comes into contact with water in the mucous membranes of the respiratory system, it produces hydrochloric and hypochlorous acids, which can cause various respiratory injuries, particularly in the upper and lower airways. High concentrations of chlorine gas can cause life-threatening lung injuries, such as lesions and sloughing of epithelial cells, as well as indirect damage to cells and tissues through the creation of free radicals. Exposure to chlorine gas can also result in the recruitment of inflammatory cells, such as neutrophils, and lead to airway hyper-responsiveness, as well as affect the vascular system and hemostasis, causing coagulation and fibrinolytic abnormalities. However, at the sub-cellular level, such as the transcriptome and proteome, there is limited information available (Clark et al. 2023)

3.1.2. Phosgene ($COCl_2$)

Phosgene, also known as CG or $COCl_2$, is a Chemical Warfare Agent that has been responsible for hundreds of thousands of deaths during World War I. Despite accounting for only 25% of all CWA production, it is responsible for 85% of CWA-related deaths. Phosgene is highly dense, with a density of 3.5 g/mL, which allows it to settle in low-lying areas and linger for extended periods. Unlike chlorine, it has a subtle odor similar to hay or grass, making it difficult to identify. The most common route of exposure to phosgene is through inhalation. Initial symptoms include a mild dry cough and skin and mucous membrane irritation. Within a few hours, typical respiratory symptoms develop, such as coughing, chest tightness, and wheezing. In severe cases, patients may develop Phosgene-Induced Acute Lung Injury (P-ALI), which can lead to pulmonary edema, hypoxemia, and difficulty breathing (fig. 1). In some cases, P-ALI can progress to Acute Respiratory Distress Syndrome (ARDS). Despite its deadly history as a chemical weapon, phosgene continues to be widely used as an organic intermediate in various industries such as chemicals, pesticides, and organic synthesis (Lu et al. 2021).

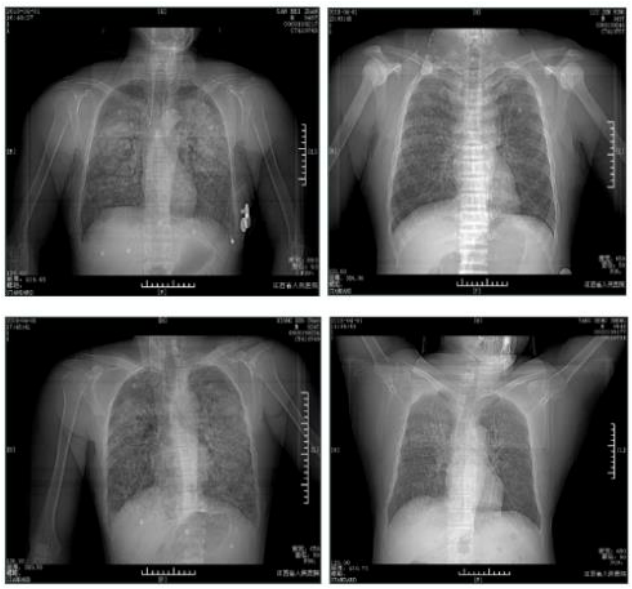

Figure 1. phosgene-induced acute lung injury. Chest x-ray shows diffuse patchy shadows in both lungs and the heart shadow size is normal (Graing et al. 2010).

3.1.3. Chloropicrin (CCl_3NO_2)

Chloropicrin, also known as trichloronitro-methane, is a colorless mobile liquid (bp 112 °C) of high volatility (1.65 3 105 mg m23 at 20 °C). It was first synthesized by combining an aqueous solution of picric acid with bleaching powder. During World War I, chloropicrin was widely used as a lachrymal-tory and lethal gas, often mixed with other toxic agents like phosgene and diphosgene. Upon inhalation, it causes vomiting, forcing soldiers to

remove their masks and expose themselves to other penetrating gases. Chloropicrin is extremely toxic, with concentrations as low as 0.8 ppm causing potentially lethal pulmonary edema. Additionally, its metabolites can be mutagenic in mammals. Although it has low solubility in water (0.16% at 25°C), chloropicrin is still used as a grain fumigant and soil insecticide, raise environmental concerns due to its continuous use. However, it decomposes rapidly in soil, with a half-life of around 4 hours. The United States conducted fumigation tests with chloropicrin as early as 1917 (Muir et al. 2002).

3.2. Blister agents

3.2.1. Hydrogen Cyanide (HCN)

Hydrogen cyanide (HCN) is a chemical compound that is used extensively in the manufacturing of synthetic fibers, plastics, dyes, pesticides, and other industrial products. However, it is also considered a toxic industrial chemical (TIC) and a chemical warfare agent due to its potential lethality. As a CWA, HCN is a nonpersistent chemical agent that can be deadly in small doses. It has been used in genocidal Nazi concentration camps, terrorist attacks, and judicial executions in some states of the USA. The low lethal dose LD_{50} for HCN is 50-60 mg for oral uptake and 1 mg for intravenous injection for a 75 kg person. HCN is a colorless to pale-blue liquid that vaporizes quickly, producing potentially lethal concentrations in enclosed spaces. The vapors are slightly lighter than air, have a faint odor of bitter almonds, and are flammable and potentially explosive. HCN is highly soluble in water and can be used as a 96% solution. Its volatility is high, and in some conditions, its vapors may decompose explosively. HCN disrupts respiration processes at the cellular level, and poisoning with HCN can be fatal through inhalation, and oral or dermal exposure, due to severe depression of the central nervous system. HCN is also an environmental hazard and can be toxic to aquatic life, with long-lasting effects (Bocos-Bintintan and Ileana 2021).

3.2.2. Sulfur Mustard ($C_4H_8C_{l2}S$)

In the course of researching the interactions between olefins and sulfur halogen compounds, the compound known as mustard gas, or bis (2-chloroethyl) sulfide, was discovered. In 1886, V. Meyer was able to synthesize a highly pure form of sulfur mustard, which is commonly referred to as HD according to the military code used in Western countries. Sulfur mustard is also known by other names, such as "typical odor" due to its distinct smell.

The effects of exposure to mustard depend on the amount and duration of exposure, and can result in damage to DNA, particularly in tissues with rapidly dividing cells such as the respiratory and gastrointestinal systems and bone marrow. Individuals with widespread involvement are at greater risk of developing sepsis, which can lead to death (Saladi et al. 2006).

Sulfur mustard is a highly significant military vesicant that was last used in the Iran-Iraq war. Unfortunately, over 100,000 Kurds were injured by sulfur mustard, and many continue to suffer from its late effects today. Exposure to sulfur mustard can cause a range of medical problems in humans, including damage to the eyes, skin (fig. 2), respiratory tract, reproductive and developmental systems, gastrointestinal tract, and blood. Additionally, exposure to sulfur mustard has been linked to an increased risk of cancer (Kehe and Ladislaus 2005).

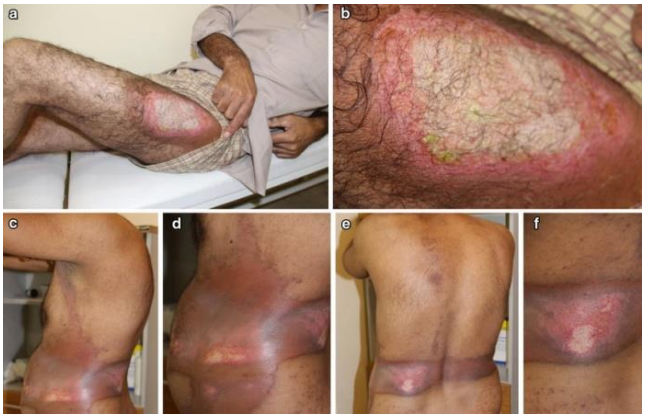

Figure 2. Skin wounds caused by exposure to sulfur mustard. Pictures of patient1 (a, b) and patient 2 (c–f) were taken two weeks after poisoning (John et al. 2019).

3.3. Riot control agents

3.3.1. O-chlorobenzylidene malononitrile (CS) ($C_{10}H_5ClN_2$)

Chlorobenzylidene malononitrile, also known as CS, is a type of riot control agent that is a variation of bromobenzylcyanide (CA) developed around 1920. Its chemical structure consists of 2-chlorophenyl-methylenepro-panedinitrile or β, β-dicyanoo-chlorost-yrene. CS can be synthesized by either condensing o-chlorobenzaldehyde with malononitrile or by condensing o-chlorobenzaldehyde with cyanoaceta-mide and then dehydrating the resulting product. It is a white crystalline powder with a molecular weight of 188 and a molecular formula of $C_{10}H_5N_2Cl$. CS has a pungent odor similar to pepper and can be detected immediately. The vapor of CS is heavier than air and has a vapor pressure of 0.00034 mmHg at 20°C. It has low solubility in water but can readily dissolve in methylene chloride (Olajos and Harry 2001).

The clinical symptoms resulting from exposure to CS gas are typically acute and short-lived. They include eye-related symptoms such as tearing, eye irritation, conjunctivitis, periorbital edema, and blepharospasm, which usually develop within a few minutes and resolve within a day. Respiratory symptoms may appear immediately or after a latency period of up to 1 to 2 weeks, and may include cough, dyspnea, hemoptysis, bronchoconstriction, and laryngospasm. These symptoms can lead to conditions such as hypersensitivity pneumonitis or reactive airways dysfunction syndrome. Patients exposed to CS gas demonstrate sustained worse lung function compared to unexposed controls, especially if they are smokers. Gastrointestinal symptoms such as diarrhea, vomiting, haematemesis, and abdominal pain have also been attributed to CS gas exposure or ingestion. Dermatological effects of CS range from mild erythema to extensive blistering and burns.

During the last large-scale deployment of CS gas in Hong Kong in 1995, burn was the most common symptom observed, with 52% of affected detainees experiencing acute burns affecting on average 3% of total body surface area. Mechanisms of burn can include flames from the explosion of tear gas grenades, contact burns from hot canisters, and chemical burns from contact with CS powder (Tsang, et al. 2020).

3.3.2. CN2-Chloroacetophenone (CN)

2-Chloroacetophenone, which is commonly referred to as CN and is primarily used as a riot control agent, can cause uncontrolled sneezing, coughing, eye irritation, and lacrimation. This compound was first synthesized in 1871 and has a long history of use in military actions. CN is also the main active ingredient in a liquid mixture known as "Mace," which is used for riot control and law enforcement. CN is a colorless crystalline solid at room temperature, with low solubility in water but high solubility in alcohols, ethers, and other organic solvents. Exposure to high concentrations of CN aerosol can cause intense ocular and respiratory irritation, as well as a burning and painful sensation in the eyes, nose, throat, and lungs. Some symptoms can persist for up to 20 minutes. The maximum safe dose for short-term inhalation of CN is 500 mg/m3. After World War I, CN began to be used as a chemical warfare agent in military operations and exercises. From the 1930s onwards, the Japanese army manufactured and shipped large quantities of CN agents, referred to as "Midori" or "green color agent," to China. At the end of the war, the Japanese army directly dumped large amounts of CN into water areas in China in an effort to cover up evidence of their criminal use. As a result, abandoned chemical agents have been found in nearly 100 locations in China (Hao et al. 2022).

3.4. Asphyxiants/ Blood agents

3.4.1. Cyanogen Chloride (ClCN)

Cyanogen chloride, also known by other names such as chlorine cyanide, chlorocyanogen, and chlorcyan, has been identified as a blood agent that forms cyanide in the body. Similar to hydrogen cyanide, it has been classified as a systemic agent or systemic poison. During World War I, both the French and British militaries utilized large quantities of cyanogen chloride. France reportedly combined the compound with hydrocyanic acid to create an irritant that would compel enemy troops to remove their protective

respirators, leaving them exposed to other toxic gases. Later in the war, cyanogen chloride was combined with arsenic trichloride. To extend its shelf life, cyanogen chloride was often combined with stabilizers like sodium pyrophosphate, as it tends to spontaneously polymerize. Although the United States stockpiled 500 and 1000 pound cyanogen chloride bombs during World War II, they were never deployed (Lukey et al. 2019).

3.5. Nerve Agents

A group of chemicals that belong to the class of pesticides and chemical warfare agents can cause seizures and convulsions in humans by inhibiting the hydrolytic enzyme acetylcholine-esterase (AChE). This category encompasses more than 200 compounds, including organophosphorus (OP) nerve agents that were developed for chemical warfare during World War II (Jett, 2012). Nerve agents that belong to the class of organophosphates are categorized into two main types: V agents and G agents. The G agents, including tabun (GA), sarin (GB), and soman (GD), were developed before or during World War II. They have chemical formulas of $C_5H_{11}N_2O_2P$, $C_4H_{10}FO_2P$, and $C_7H_{16}FO_2P$, respectively. In the early 1950s, the V agent VX was developed with a chemical formula of $C_{11}H_{26}NO_2PS$. VX contains two oxygen atoms bonded to its central phosphorus atom and the sulfur atom of its phosphonothiolate group. VX is less volatile than G agents, making it more persistent.

The seizure-inducing activity of organopho-sphate (OP) and carbamate cholinesterase inhibitors arises from the inhibition of the hydro-lytic enzyme acetylcholinesterase (AChE), which leads to a buildup of the neurotransmitter acetylcholine (ACh) and overstimulation of cholinergic synapses in the brain. Seizures can originate in different regions of the brain and spread, causing damage to various areas such as the cortex, hippocampus, thalamus, and amygdala. The overstimulation of postsynaptic muscarinic ACh receptors triggers epileptiform activity and activation of glutamate receptors, both of which cause an increase in intracellular calcium, other physiological and metabolic effects, and ultimately, neuropathological changes. Acute OP poisoning can lead to chronic neuropathological sequelae due to the initiation of neurodegenerative processes driven by excitotoxic and neuroinflamm-atory responses. Evidence suggests that Gulf War veterans and victims of terrorist attacks in Japan may have experienced long-term effects from exposure to nerve agents and pesticides (Jett 2012).

3.5.1. 3-Quinuclidinyl benzilate ($C_{21}H_{23}NO_3$)

BZ is a white crystalline substance that has a bitter taste and can dissolve in both aqueous and organic solvents. It remains stable under field conditions for at least 1 or 2 days with no reduction in its incapacitating activity. BZ is effective when administered through all routes and gets metabolized primarily in the liver and excreted through the kidneys. After exposure to an effective dose, mild peripheral effects occur within an hour, and central effects occur after approximately 4 hours. BZ can be absorbed through different routes, including oral, parenteral, and inhalation. When administered through inhalation, the absorption into the bloodstream is more pronounced compared to oral administration. This compound binds to plasma proteins, mainly albumin, and gets transported to the CNS and PNS, where it interferes with cholinergic nerve transmission at muscarinic sites in the peripheral autonomic nervous system, brain, and spinal cord. Due to the wide distribution of muscarinic receptors, the effects are observed in almost every phase of neural regulation. BZ can easily cross the blood-brain barrier (BBB) and get distributed to all areas of the brain and spinal cord, where it interacts with cholinergic receptors as a competitor of the physiologically active neurotransmitter ACh. This effect results in a relative lack of acetylcholine. At the periphery, BZ binds to acetylcholine muscarinic receptors, similarly to atropine, with a strong antagonistic effect on the receptors. BZ binds to all subtypes of muscarinic receptors (M1-M5) present in the ACh. Each subtype exhibits different functions in the brain. The long-lasting central effects of BZ may be due to its high affinity for nervous tissue, especially its strong adsorption by mitochondria. This property of BZ

leads to a decrease in oxygen consumption by nerve cells (Fusek et al. 2020)

3.6. Smoke materials

3.6.1. White phosphorus (WP)

White phosphorus is a combustible solid that appears waxy, yellow, and transparent, and it's primarily utilized in military and industrial environments to produce smoke. When exposed to oxygen, it ignites spontaneously and emits a yellow flame that generates thick smoke. It can only be extinguished by depriving it of oxygen or allowing it to burn out entirely. Direct contact with white phosphorus can cause painful chemical burns on the skin. Weapons containing white phosphorus are available in various forms, including bombs that are dropped from aircraft, artillery shells, and grenades. White phosphorus has a spontaneous ignition point of 44 degrees Celsius in the air and produces flames that can reach temperatures of 800 degrees Celsius or up to 816 degrees Celsius when in contact with oxygen (Christensen 2016).

Upon contact with human skin, WP can cause both chemical and thermal burns. The heat generated from the reaction causes thermal burns, while chemical burns result from the production of several compounds. One of these compounds is phosphorus pentoxide, which can react with the water in the skin and produce corrosive phosphoric acids. WP burns can cause serious damage to internal organs and even death. The chemical burns can penetrate deep into underlying tissues, resulting in delayed healing. When WP is applied to burn wounds, it can be absorbed into the body systemically, leading to multiple organ dysfunction syndrome. This is due to the harmful effects it has on vital organs such as erythrocytes, kidneys, liver, and heart. Additionally, the inhalation of WP smoke can be hazardous to human health. When WP combusts, it creates phosphorus pentoxide, which is a severe pulmonary irritant. In a confined space, the concentration of phosphorus pentoxide may reach levels that are high enough to cause acute inflammatory changes in the tracheobronchial tree (i.e., the airways of the human respiratory system) (Christensen 2016).

White Phosphorus (WP) has been used as a weapon of warfare in various conflicts, including World War I, World War II, Grozny, Chechnya in 1994, and recent conflicts in Ethiopia, Iraq, Afghanistan, and Israel. Its military application is increasing, and it is used by both State and non-State actors. WP has been banned for use against civilians, but it is still legal for use as an obscurant or for marking targets (Christensen 2016).

4. Biological weapons

The definition of biological weapons by the WHO states that they achieve their intended effects through the use of disease-causing microorganisms and other entities, including viruses, infectious nucleic acids, and prions. The 2004 WHO guidance specifically addresses the impact of these pathogens on human beings. Biological warfare (BW) is typically conducted by nation states with the objective of undermining the opponent's will and capabilities to retaliate. This can involve deliberate actions to cause illness or death among the opponent's armed forces, population, crops, and livestock through the release of biological agents (Jansen et al. 2014).

The Centers for Disease Control and Prevention (CDC) has categorized Bioterrorism Agents/Diseases into two main categories based on their potential threat level. Agents classified as Category A bioterrorism agents are considered the most critical due to their ability to be easily transmitted from person to person, their potential to cause high mortality rates, their capacity to cause significant public health impact, their potential to induce public panic and social disruption, and the need for special measures in public health preparedness. Category B bioterrorism agents, on the other hand, are ranked as the second highest priority. While they are still relatively easy to disseminate, they generally result in moderate morbidity rates and low mortality rates. However, specific enhancements of the Centers for Disease Control and Prevention's (CDC) diagnostic capacity and disease surveillance are required to effectively address them.

Table 1 presents the key examples of microorganisms utilized as biological weapons, as per the CDC classification.

Table 1. The key examples of microorganisms utilized as biological weapons

Agents	Diseases	Category
Bacillus anthracis	Anthrax	A
Clostridium botulinum toxin	Botulism	A
Yersinia pestis	Plague	A
variola major	Smallpox	A
Alphaviruses	Viral encephalitis	B
Filoviruses (Ebola)	Viral hemorrhagic fevers	A
Vibrio cholerae	Water safety threats	B
Clostridium perfringens	Epsilon toxin	B
Rickettsia prowazekii	Typhus fever	B

5. Decontamination approaches of Chemical and biological agents

Decontamination is defined as the process of removing or neutralizing chemical agents from people, equipment, and the environment. In order to minimize the damage and consequences of chemical and biological terrorism, decontamination is vital to quickly clean up victims, facilities and equipment. The type and level of decontamination depends on the physical properties of the agent as well as the route of exposure and it can be grouped into two main classes: (i) physical and (ii) chemical decontamination.

5.1. Physical decontamination

Disrobing (removing the outer layers of clothing) is the first line of physical decontamination.

Rapid intervention using any readily available absorbent material such as tissue paper, diapers, sanitary pads, cotton wool, or toilet paper especially in civilian decontamination (Kassouf et al. 2017).

Mechanical wiping action with large volumes of water is the second line of physical decontamination (Chilcott et al. 2018; Lake et al. 2009).

5.2 Chemical decontaminants

Bleaching powders. HTH (high test hypochlorite), STM (super tropical bleach), Dutch powder, ASH (activated solution of hypochlorite), and SLASH (self-limiting activated solution of hypochlorite) are using as bleaching powders. The bleach must be fresh and for complete inactivation of agent, it must be prepared on a large scale.

Solution decontaminant. Decontamination solution 2 (DS2) consists of 28% ethylene glycol monomethyl ether, 70% diethylenetriamine, and 2% sodium hydroxide.

Other properties of the decontaminant are long term stability, a large operating temperature range (26-52 °C), corrosive for the skin and flammable and cannot be used with bleach or other strong oxidizing agents. However, solutions with 0.5% hypochlorite are contraindicated for the eye, as they may cause corneal injuries. Also they should not be used in open wounds (Hurst 1997). Dakin's solution, consists of sodium hypochlorite (0.4–0.5%) and boric acid (4%). DIPHOTERINE® solution for eye decontamination is an emergency rinsing solution for splashes of chemical products on the skin or in the eye in order to limitation the extent of the burns and lesions caused. Diphoterine is a polyvalent, hypertonic, amphoteric, chelating liquid and it can reduce the amount of stromal edema compared with water. It work better than soapy water and physiological saline in decontamination of sulfur mustard but not effective against HD (Braue, 2007). Modec Decontamination Foam (MDF-100) contains two solutions. When the two solutions were mixed and sprayed, they generated foam. MDF-100 supplied good protection against soman and VX exposure but it can't neutralize anthrax spores with sufficient speed (Clarkson et al. 2012).

Decontamnation kits. M258 kit, M258A1 and M280 are skin decontamination kits. These kites consist of two packets, one containing a towelette prewetted with a solution of 10% phenol, 72% ethanol, 5% sodium hydroxide, 0.2% ammonia, and 12% water by

weight. Another towelette is impregnated with chloramine-B and accompanied by a sealed glass ampule filled with a 5% zinc chloride solution. These kits are effective against G agents. M291 and M295 kits as a skin decontamination kit include nonwoven fiber pads filled with resin mixture (Ambergard XE-555) that provide a high surface area. The primary effectiveness of kits depends on the physical removal of the agents by wiping. RSDL kit containing six separate decontaminating pads, each pad were designed to absorb and neutralize liquid CWAs.

Decontaminant lotion. Reactive skin decontaminant lotion (RSDL) that is effective against V- and G-type NAs and contains an alkali metal salt of phenol, acetone oxime, acetophenone oxime, 2,3-butanedione monoxime, and tetraglyme as a solvent.

Microemulsion. C8, a microemulsion system, contains 15% tetrachloroethylene (C_2Cl_4) which serves as the continuous phase (water is dispersed in organic tetrachloroethylene liquid system), 76% water, 1% anionic surfactant, and 8% $Ca(OCl)_2$. MCBD, a microemulsion system, contains 60% water, 7% tetrachloroethylene, and 28% CTAC (n-cetyl trimethylammonium chloride), and $(nBu)_4NOH$ as a cosurfactant.

Decontamination Sponge. Reactive polymer sponges, polyurethane sponges and immobilized enzyme sponges are synthetic sponges incorporating scavenging enzymes (cholinesterase enzymes and oximes) and detoxifying chemicals that they can stoichiometrically interact with agents and detoxify organophosphate agents. They are more effective, self-contained, easy-to-use, field-deployable, self-use decontamination devices. The immobilized enzyme sponge is used to detoxify organophosphate toxins. One limitation in large-scale deployment of these sponges is the limited amount of available enzyme. Polyamines are the other group of sponges which provide reactive nucleophiles for sulfur mustard alkylating agents, and tetraglyme to extract the CWAs from skin and wounds. Generally sponges are more efficacious and medically safe than other decontaminants such as RSDL and M291 for soman and VX (Gordon et al. 2006). H257Y/L303T with phosphotriesterase mutant enzyme and a PCB polymer coating is highly effective against sarin and it has made possible the development of a prophylactic treatment with long lasting circulating (Bigley 2019).

Decontamination fabrics. Polyitaconic acid as a fabric with the neutralizing capacity can be significantly effective for the skin decontamination of a chemical warfare agent simulant, as well as soman, HD, and VX (Matar et al. 2015).

Decontaminants must be lightweight, readily available, non- offensive odor and residue, nonirritating to eyes or lungs, nonallergenic, medically and environmentally safe.

5.3. Skin decontamination

Quick diagnosis of a CWA exposure is the first step in the skin decontamination process (sooner recognition, less penetration of agent and finally less damage). In military, applying of barrier creams (such as SERPACWA) as a topically protectants is effective against the toxic effects of CWAs. Because of less effective against vapor hazards, SERPACWA was withdrawn from service in 2011 and replaced by Antigas-7 (AG-7) that has good efficacy against liquid CWAs and also against sulfur mustard vapor (Chilcott et al. 2007). After diagnosis, the outer layers of cloths must be removed. Wrapping of cloths and wiping off the liquid nerve agent with clinical towels ("blue roll") or microfiber cloths will limit further internal/external contamination of the patient and staff. All removed clothes and jewelry must be placed in a double bag and sealed and left cordoned in a well-ventilated area to prevent accumulation of any off-gassing agent. This early spot decontamination can be done simultaneously during clinical evaluations such as breathing, hemorrhage and other problems in the patient. With observing of life-threatening injuries such as airway compromise or life-threatening catastrophic haemorrhage in a patient, this should be checked as a priority in the ‘Hot Zone’ before decontamination. Early detection of the toxidrome allows early antidotes to be administered that will save lives. In liquid nerve agent poisoning, dry and then wet decontamination are more recommended (Hulse et al. 2019). The quickly physical removal of the chemical agent from

the skin (e.g. soapy water and wet tissue paper) is very important before decontamination. The main effect of water and soapy-water is the physical removal or dilution of agents; however, CWAs have low solubility and slow rate of diffusion in water that limit the agent hydrolysis, particularly with alkaline soaps (Hurst 1997). Therefore, water-only or water and soap yield partial decontamination of CWA and other chemical decontaminants are needed (Chiang et al. 2022). In decontamination of CWAs such as sulfur mustard, GF and sarin, since undiluted bleach causes skin damage, it is necessary to use diluted bleach to 0.5% hypochlorite for decontamination (Hobson and Snider 1992). Liquid skin decontaminants such as RSDL, DS2, DIPHOTERINE® and other decontaminants (powders, kits, lotions and etc.) if available can be used for skin decontamination. Studies showed that RSDL is superior to the M291 kit, 0.5% hypochlorite solution, and soapy water against a broad spectrum of agents, including soman, cyclosarin, VX, and VR and it ranked last in decontaminating sulfur mustard in compared with Dutch Powder, Fuller's earth pad, and M291 kit (Braue et al. 2016). RSDL approved as a medical device for neutralizing the effects of many agents, including VX, G series agents, sulfur mustard, and T-2 fungal toxin (FDA 2003).

5.4. Wound decontamination

Many standard forms of antidotes, such as RDSL are contraindicated for use on wounds (Graham et al. 2008; Walters et al. 2007). Bleach solutions have been considered as a potential device of wound decontamination. However, concentration of bleach and the applying method is very important in wounds decontamination. Studies showed that in wound decontaminated with sulfur mustard, decontamination with 0.5% hypochlorite and even water soaking for 5 min caused greater necrosis than when no decontamination was carried out. Or the other study showed that in wound decontaminated with VX, the 0.5% bleach is not effective in increasing survival rate; whereas 5% bleach increase the median lethal dose twofold. In non-compressible hemorrhaging wounds, the bleeding should be arrested and any CWA within the damaged tissue should be neutralized simultaneously.

A small number of hemostatic products have been identified that also exhibit CWA decontamination capability. WoundStat™ as a wound decontaminant is a clay-based, granular hemostatic agent that is most effective against multiple vesicating doses of HD and GD or VX (Dalton et al. 2018).

6. Detection of BCWs

Monitoring the presence of BCWs in the infected humans generally involves assaying biomedical samples. The body attempts to quickly rid itself of a BCW by metabolizing it to a water-soluble form, where it is rapidly excreted through the urine. These urinary metabolites are used as markers of BCW exposure. However, the opportunity to detect these urinary metabolites is limited by the time course of urine clearance (Brian et al. 2019). The early methods focused mainly on gas chromatography-mass spectrometry (GC-MS) analysis of metabolites in urine after exposure.

The longest-lived markers are those resulting from the interaction of the agent with large molecular weight targets, such as human serum albumin (HSA), butyrylcholinesterase (BChE), and DNA, and form macromolecular adducts (Brian et al. 2019). Blood/plasma analysis offers potential advantages, as both longer-lived macromolecular adducts and unbound metabolites can be assayed.

6.1. Nerve Agents

Most of the nerve agent assays are based on determination of either activity of cholinesterase (ChE) enzymes or levels of nerve agent metabolites (Black and Read 2013; Langenberg et al. 2009). Several non-cholinesterase analytical methods such as mass spectrometric detection techniques with liquid chromategraphic (LC) or gas chromatographic (Brian et al. 2019), tandem MS (MS-MS) (Barr et al. 2004), flame photometric detection (FPD) and high-resolution MS (HRMS) (Zydel et al. 2012) have been developed to confirm exposure to nerve agents.

Fidder et al. 2002 reported a method based on organophosphorus (OP) binding to BChE, which involves immunomagnetic capture of the BChE from plasma and digestion of BChE to produce nonapeptide fragments containing the serine-198 residue to which OP is bind. The analysis of nonapeptides employs LC-MS/MS techniques. For the fluoride-induced reactivation of protein-bound nerve agent, GC-CI-MS or GC-EI-MS/MS (where CI is chemical ionization and EI is electron impact ionization) were used. For the BChE adducts, LC-HRMS and LC-MS/MS were used (Fidder et al. 2002). Sulfur Mustard (HD) produces reactive sulfonium ion that can combine with macromolecules (Black and Noort 2005). Some methods focused on unmetabolized Sulfur Mustard or on the non-unequivocal biomarker TDG. So, urine is treated with concentrated hydrochloric to convert TDG back to HD, followed by GC-MS analysis with a thermo desorption cold trap injector (Riches et al. 2007).

Approaches to measure HD adducts to DNA macromolecules in white blood cells have been developed using HPLC-ESI-MS/MS in MRM mode, LC with fluorescence detection, and using an enzyme-linked immunosorbent assay (ELISA) (van der Schans et al. 2008; Schulze et al. 2016). In the research by Liu et al. 2015, plasma protein was digested by proteinase K and Cys*-Pro-Phe directly analyzed by UHPLC-MS/MS without solid phase extraction.

6.1.1. Cyanide

At low concentrations, cyanide is bound to met hemoglobin (metHb). Prior to analysis, cyanide is separated from metHb using sulfuric acid, and followed analyzing by GC-nitrogen phosphorus detector (NPD) (Brian et al. 2019).

6.1.2. Phosgene carbonyl chloride ($COCl_2$)

Phosgene can react with proteins of blood, including hemoglobin and albumin. It also reacts with glutathione (GSH) to form an acylated dimer called diglutathionyl dithiocarbonate (GSCOSG). Some analytical methods include isolation of the albumin by affinity chromatography, dialysis, carboxymethy-lation, and tryptic digestion followed by μLC-MS/MS on either MRM on a triple quadrupole MS or a high-resolution MS on a quadrupole time of flight (Q-TOF) (Brian et al. 2019).

6.1.3. Biological pathogens and biotoxins

Compared to CWAs, biotoxins and biological pathogens are effective in very low doses, and they are odorless and colorless. Biological analysis is different from chemical analysis, and one of the major problems during the analysis of biological agent is the natural biological background. An aerosol particle sizer (APS) is a simple form of sensor that can detect airborne particles within a defined hazardous size range, and utilize matrix-assisted laser desorption/ioniza-tion time-of-flight (MALDI-TOF) for more analysis.

Approaches based on Enzyme-linked immune-sorbent assay (ELISA) utilize the high affinity and specificity of antibodies to target viruses, bacteria, and toxins of interest. For this purpose, the technology of producing different polyclonal and monoclonal antibodies based on the type of biological agent is very important. Also, the Polymerase chain reaction (PCR) assay can detect microorganisms in a short period of time and real time-PCR is today the most applied technique for the identification of microbial agents.

Raman spectroscopy and surface-enhanced Raman scattering (SERS) are suggested approaches for identifying pathogens, nucleic acids, and biotoxins (Langer et al. 2020). New optical spectroscopic techniques and label-free biosensors (fig. 3) that allow real-time biological monitoring are next-generation approaches. Lab-on-a-chip technologies, known as microarray or microchips, offer the possibility to analyses several microorganism and biotoxin on a single microchip.

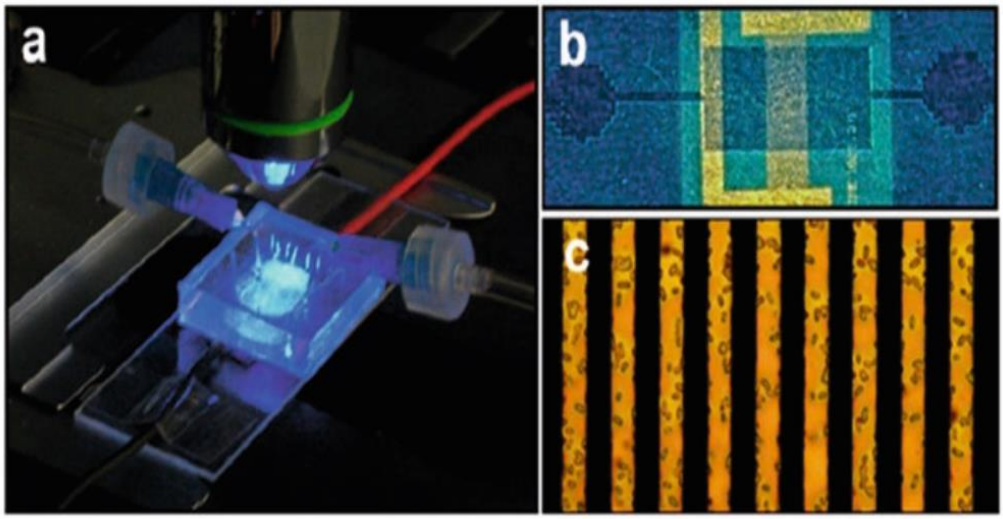

Figure 3. Real-time binding of bacteria to AMP biosensors (Mannoor et al. 2010).

Electronic transduction of biological and chemical reaction enables a Field-Effect Transistor (FET) to possess sensitive detection as a biosensor. Machine-learning (ML) allows researchers to analyze complex signals generated by FET sensors and fabricate high-quality sensors. Some ML algorithms, including SVM, PCA, and ANN, were utilized for identifying unknown substances and determining the concentration of target analyte (Jae-Hyuk 2014).

7. Treatment

Of the potentially lethal chemical agent, nerve agents have specific antidotes (such as atropine, diazepam, pralidoxime (2-PAM) chloride, and pyridostigmine bromide). Some soldiers carry four auto injectors for intramuscular injection. Three combination autoinjectors, which each include 600 mg of 2-PAM chloride (1800 mg total) and 2 mg of atropine (total 6 mg) are called antidote treatment nerve agent autoinjector (ATNAA), and its civilian equivalent is called Duodote. Diazepam, 10 mg, is provided in the fourth autoinjector called convulsive antidote, nerve agent (CANA). Additionally, pyridostigmine bromide (PB) pills in 30 mg are considered against nerve agent soman (GD). Pyridostigmine is applied as a pretreatment and is recommended to be taken before soman (GD) exposure. It is ineffective unless diazepam therapy and standard ATNAA are also used. Midazolam has already been discussed as a substitute for diazepam and is the better product for neurogenic seizures.

Oximes agents such as pralidoxime chloride can bind to the nerve agent that inhibits cholinesterase enzyme and break the agent -enzyme bond to release enzyme and restore cholinesterase activity. Pretreatment with pyridostigmine and application of diazepam can decrease seizure activity. Atropine does not cross the blood-brain barrier until a dose of 12 mg is received, but scopolamine rapidly crosses this barrier and treats nerve agent seizures effectively. Currently, cyanide antidotes are sodium nitrite, hydroxocobalamin, and sodium thiosulfate, which are given by intravenous (IV) infusion.

In case of Organophosphorus poisoning, treatment consists of administering a combination of pyridinium aldoxime, which acts as a nucleophile to reactivate phosphorylated AChE, anticonvulsant (diazepam), and atropine as a muscarinic antagonist to prevent excessive effects of acetylcholine.

Reactive Skin Decontamination Lotion (RSDL) is an FDA-approved medical device that decontaminates the skin, after exposure to biological/chemical warfare agents such as soman (GD), sulfur mustard (HD), and VX as well as T2 mycotoxins (Brian et al. 2019). The lotion ingredients include potassium, 2.3-butanedione mono-oxime dissolved in a vehicle of polyethylene glycol ether in water that enhances the

reaction of decontamination between the chemical agent and the oxime.

The current chemotherapy regimen may prevent death but not post-exposure complications such as behavioral abnormalities and brain damage. Betapudi et al. 2020 demonstrated that an adeno-associated virus–mediated paraoxonase 1 variant IF-11 gene therapy provides asymptomatic prophylactic protection in mice against sarin, tabone, cyclosarin, and soman in mice.

In another study a dual-expression system-based multi pathogen DNA vaccine that encodes the HCt gene of C. botulinum and the PA-D4 gene of *B. anthracis* was developed. When the multi pathogen DNA vaccine was administered to guinea pigs, increased level antibody production was observed against both HCt and PA-D4 (Kim et al. 2022).

Exposure to phosgene can lead to acute lung injury (ALI), so effective treatment for the patients with ALI caused by phosgene is needed. The therapeutic potential of mesenchymal stem cells (MSCs) in phosgene-induced ALI was evaluated, and the results showed that MSC treatment significantly reduced the severity of phosgene-induced ALI in mice (Chen et al. 2015). Moreover, in a study by Xu et al. 2019 MSC-derived exosomes were isolated from MSCs. The results showed that exosomes exert beneficial effects on phosgene-induced ALI by inhibiting MMP-9 synthesis, modulating inflammation and increasing SP-C levels.

A phosphotriesterase mutant entitled C23, engineered to hydrolyze and degrade toxic isomers of VX agents was reported in 2014 by Work et al. In this study, an in vivo guinea pig model was developed to determine the efficacy of treatment with C23 against VX poisoning. Intravenous C23 injection 5 min after challenge with VX prevented systemic toxicity, and the PTE mutant C23 was suggested as a catalytic bioscavengers for post-exposure therapy of V-agents poisoning.

8. Conclusion

There is great potential for further development of BCW agents based on modern technical methods. This risk is even greater due to the fact that there is a public acceptance of the development of non-lethal BCWs at a higher technological level. It can be assumed that in the future, new forms of BCWs will occur that will be synthesized and produced by the virtual design and synthesis of new toxins from uncontrolled agents.

It is very necessary to have good information about BCWs types, improve decontamination and detection methods, and therapies for BCW-exposed peoples and animals.

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