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Chemical warfare agent detection: a review of current trends and future perspective

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1. ABSTRACT

The World Health Organization recommends countries to create a public health system that can respond to the deliberate release of chemical warfare agents (CWAs). Procedures for preparedness, response, decontamination protocols and medical countermeasures against CWA attacks are described. Known CWAs, including their properties and pharmacological consequences upon exposure, are tabulated and discussed. Requirements imposed on detection systems by various applications and environmental needs are presented in order to assess the devices for detection and identification of specific CWAs. The review surveys current and near-term detection technologies and equipments, as well as devices that are currently available to the military and civilian first responders. Brief technical discussions of several detection technologies are presented, with emphasis placed in the principles of detection. Finally, enabling technologies that form the basis for advanced sensing systems and devices are described.

2. INTRODUCTION

The terrorist events of September 11, 2001 brought to realization the preparedness of the US government against terrorists attack. The anthrax attack that shortly followed further demonstrated the capabilities of rogue states and terrorist organizations in disseminating extreme biological or chemical warfare agents. Despite the Domestic Preparedness (DP). program established by the Department of Defense (DoD). in 1996(1), the readiness of our operations to respond to Chemical, Biological, Radioactive and Nuclear (CBRN). terrorism events was put to test. Implications of biological and chemical weapons attack seemed an inevitable scenario that the government has to proactively implement a defense readiness program. The implementation of the international treaty Chemical Weapons Convention (CWC). in 1997 may have banned the production and use of chemical agents, but adherence of all countries involved remains questionable (2). Often under-emphasized is the fact that the acquisition, proliferation and modernization of biological and chemical

warfare agents may be easier than perceived. Therefore, efforts are continually being made to fortify the biochemical defense of domestic and international governments alike (3)

Chemical warfare agents are manufactured chemicals intended to incapacitate targets and can be lethal and potent, like the notoriously known nerve gases. This review will provide an overview of chemical warfare agents (CWAs), classification, brief description of each class and known adverse effects upon exposure. Countermeasures that currently constitute protocols of the DoD, military strategists, first responders and medical personnel will also be discussed. These countermeasures range from the lessons learned from previous bio-chemical warfare attempts and attacks, both domestic and overseas, to the best preparedness programs outlined in anticipation of future intentional CWA release events. Review of open-literature (unclassified). analytical methods, technologies and commercially available systems for monitoring and early detection of chemical agents is presented. Survey of currently available systems will cover devices that have applications for use by the medical group, government defense groups, military and civilian first responders. This review could not possibly encompass all the aspects of chemical detection technologies but will preview the needs of future devices for real-time detection and identification of CWAs. Furthermore, the review will be limited to detection systems and analytical methods and technologies that have been released on or before 2009.

3. CHEMICAL WARFARE AGENTS

CWAs are chemicals intended to be used in a warfare scenario as weapons, whose toxic effects cause temporary incapacitation, permanent health damage and even death (2, 4-8). Such chemical agents may be used for civil and legitimate purposes, but when utilized in hostile settings, these agents are regarded as weapons. As weapons of mass destruction (WMD), CWAs have the potential to inflict devastation and casualties in magnitudes almost impossible to comprehend.

CWAs are fast-acting substances that can generally be classified according to the primary intended effect: harassing, incapacitating and lethal (9). Harassing agents, more commonly known as riot-control agents (RCAs), typically cause disabling effects, temporary pain and discomfort. Victims are completely aware of the situation and may be capable of evacuating from the exposure area unassisted. Victims may not require medical treatment considering the exposure is low dose and occurred in a short period of time. On the other hand, incapacitating agents cause disabling effects and are more accurately described as psychoactive chemicals. Victims are rendered totally unaware of their condition and cannot function in a cohesive manner. Therefore, victims may be incapable of evacuating from the contaminated area without assistance. Recovery without medical aid is possible, although the effects of CWA exposure may reside over a prolonged period. Lethal agents are initially physically disabling but may cause permanent health injury and, oftentimes, death at lethal doses. Each class of agents presents different physiological effects on the targets and will require a unique set of medical countermeasure. However, factors like the dose and time of exposure and individual health circumstance also need to be considered in assessing the susceptibility of a victim to adverse effects and hence, in designing a treatment protocol.

Generally, CWAs are thought to be "gaseous" but these agents exist mostly as liquids or solid particles. Of these forms, aerosolization is the most effective way to deliver CWAs. The agent can easily be disseminated as a pure substance in solid or liquid form or as an aerosol, which consists of colloidal solid or liquid particles suspended in water or other solvents. Release of aerosolized samples allows the particles to remain airborne for an indefinite period. The dissemination procedure for a specific type of agent can be designed according to the intended routes of physiological entry. Delivery methods vary according to the target population, location, and extent of destruction. Stability of the chemical agents and environmental factors are usually considered in the dissemination method and estimation of the possible effects on the victims. For instance, there are several chemical agents that are persistent (*i.e.* low vapor pressure), making skin contact as the likely route of exposure (2, 4, 10). On the other hand, chemicals that are highly volatile present the highest risk of exposure via respiratory, oronasal and conjunctiva mucosal tissues, especially if released in confined quarters (9, 11). Initial localized effects, such as irritation in the eyes and nose, can immediately take effect followed by, depending on the dose exposure, the prevalence of systemic effects.

3.1. Riot-control agents

Riot-control agents (RCAs). or "harassing" agents are chemicals that rapidly cause irritation following exposure of all oronasal and conjunctiva mucosal tissues and respiratory tract. As the name implies, law-enforcement agencies use these substances mainly "to render a person incapable of either aggression or resistance for a limited time without permanent injury."(12). As harassing agents, RCAs are considered less-lethal or non-lethal, and are "safe" in the context of causing only a brief duration of intense discomfort and temporary disabling with no long-term health effects. Other factors such as dissemination method, dosage and environment, should be considered in assessing the health effects of RCAs.

Pepper spray and *tear gas* are among the well known riot-control agents used by military and law-enforcement personnel. *Pepper spray* consists of oleoresin capsicum (OC). as the active ingredient, a mixture of naturally occurring substances extracted from capsicum plants like chili peppers, cayenne pepper, red peppers and jalapenos (13). The main irritant in OC is capsaicin (Figure 1A), a colorless solid with a pungent and irritating odor. *Tear gas* consists of *ortho*-chlorobenzylidene-malononitrile (CS). (Figure 1B). as the main component. CS is also known by other names such as 2-chlorophenyl-methylene propanedinitrile, β,β-dicyano-*o*-chlorostyrene, or 2-chlorobenzal malonitrile (13). It is a white crystalline solid

Table 1. Physical and chemical characteristics of *oleoresin capsicum* (OC) and *ortho*-chlorobenzylidene-malononitrile (CS) (13-15)

Properties	OC	CS
CAS #	404-86-4	2698-41-1
MW	305.41	188.6
Molecular Formula	$C_{18}H_{27}NO_3$	$C_{10}H_5ClN_2$
Physical State[1]	Colorless solid	White crystalline solid
Odor	Pungent, irritating	Pungent pepper-like
Skin and eye effects	Sensation of intense pain and burning due to the activation of TRPV1 sensory neuron releasing substance P; Lacrimation, eye redness and burning sensation, and blepharospasm; causes dermatitis at excessive exposure	Skin irritation, itching, stinging, erythema; blistering and dermatitis; lacrimation, burning sensation and blepharospasm
Respiratory effects	Coughing, decreased inhalation rates; pain, vasodilation, secretion in the airways	Salivation, coughing, choking, chest tightness; may cause reactive airway disease syndrome (RADS) requiring medical intervention
Decontamination	Move to fresh air. Flush face with cool water; if burning persists, use ice pack. Do not rub area. Decontaminate required areas with soap and water.	Move to fresh air. Flush eyes and skin with water. Do not rub eyes. Do not use oil-based lotions. Do not use any form of bleach. Use soap and water on equipment contaminated with CS, CS1, or CS2.7
Toxicity (mg min/m^3)	LCt_{50}: N/A	LCt_{50}: 52,000-61,000[2] (provisional)

[1] at room temperature and pressure; [2] based on existing human estimates

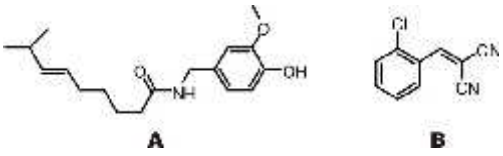


Figure 1. Molecular structures of A) capsaicin and B) *o*-chlorobenzilidene- malononitrile (CS) (13).

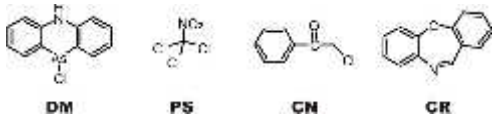


Figure 2. Molecular structures of diphenylaminearsine (DM), chloropicrin (PS), *ortho*-chloroacetophenone (CN), and dibenzo (*b,f*)-1,4-oxazepine(CR) (13-15).

with a pungent, pepper-like smell. CS is the most commonly used riot-control agent by law enforcement and military agencies for trainings, to quell demonstrations and unruly subjects, crowd control and in rescue operations. Other riot-control compounds with less- to non-lethal effects are *ortho*-chloroacetophenone (CN), dibenzo (*b,f*)-1,4-oxazepine(CR), diphenylaminearsine (DM). and chloropicrin (PS). (Figure 2). A formulation of CN, also known chemically as *m*ethyl chloro*ace*tphenone, and capsaicin are the known components of *mace*, an alternative riot-control agent.

Riot-control agents have low vapor pressure and are therefore usually disseminated as fine powders or aerosol sprays. Common to all riot-control agents is the low dose needed for rapid and intense pain. CS specifically affects the peripheral and sensory nerve endings of the mucous membranes and skin, causing irritation and intense pain (Table 1). (13-15). Upon exposure to OC, toxicology studies showed a sudden release of the neurotransmitter bradykinin or substance P, signaling the sensation of intense pain (16). Dermatological effects, such as allergic rashes, burns, blisters, dermatitis and intense burning pain, are also noted upon exposure to riot-control agents. Effects of eye exposure are irritation, inflammation, conjunctival swelling and burning sensation. These effects are accompanied by lacrimation or intense tear production, involuntary eyelid closure and temporary blindness (13). Inhalation of riot-control agent manifests respiratory and ventilator depression effects, such as intense coughing, throat irritation, choking, difficulty breathing and chest pain (14). Irritation and burning sensation in the nose and mouth followed by salivation and excessive nasal discharge are also among the most common symptoms. Maximum effects occur within 20–60 seconds after exposure and can persist for 5–10 minutes (5). Although the onset of exposure and effects is almost instantaneous, symptoms completely improve within 30 minutes after the victim is removed from the contaminated environment (13)

The National Institutes of Occupational Safety and Health (NIOSH). and Occupational Safety and Health Administration (OSHA). have reported a safety limit of exposure to CS at 0.4 mg/m^3 and the value of immediate danger to life and health (IDLH). is 2 mg/m^3 (13, 17). On the other hand, the lethal dose of OC in human has been shown to be between 0.5 to 5.0 g/kg (13, 18). A significantly high dose of exposure to these agents can cause long-term disabilities or even death. Higher dose exposure can cause severe skin irritations, blisters and erythema, as well as ophthalmic complications like glaucoma, cataracts, infective keratitis, traumatic optic neuropathy and hemorrhage (13). Reactive airway disease syndrome (RADS), often accompanied with prolonged coughing and difficulty breathing,(13). is one of the known long-term respiratory effect and complication arising from excessive exposure to riot control agents.

3.2. Incapacitating agents

Incapacitating agents that are intended to be used in a warfare scenario, although still categorized as non-lethal, mainly target the central nervous system. The effects of these agents are temporary, and risks are minimal for long-term side effects after exposure to normal doses. Chemical agents under this group are considered mind-altering chemicals causing mental and physiologic effects. Exposure to these agents, sometimes referred to as "psychochemicals", render the exposed targets disoriented, incapable of normal functioning and unaware of their situation. The symptoms may last for hours and even days

Table 2. Properties of incapacitating agents (20-22, 30, 31)

Properties	Fentanyl	LSD-25	BZ
CAS #	437-38-7	50-37-3	13004-56-3
Molecular Formula	$C_{22}H_{26}N_2O$	$C_{20}H_{25}N_3O$	$C_{21}H_{23}NO_3HCl$
Molecular Weight	336.48	323.43	337.4
Physical State[1]	White powder or solution	Colorless solid	White, crystalline solid
Odor	None	None	None
Toxicity	3.1 mg/kg (rats) (LD_{50})	200 μg/kg to 1 mg/kg human body mass (LD_{50})	3,800-40,000 mg·min/m^3 (LCt50)
Signs and Symptoms of Exposure	Respiratory depression; slow pulse; lethargy; sedation; immobilization	Restlessness; dizziness or giddiness; erratic behavior; stumbling; vomiting	Dryness in mouth, slow pulse; elevated temp; blurred vision; slurred speech; dilated pupils; restlessness; giddiness; confusion; erratic behavior; vomiting, staggering; hallucinations; stupor and coma

([1] at room temperature)

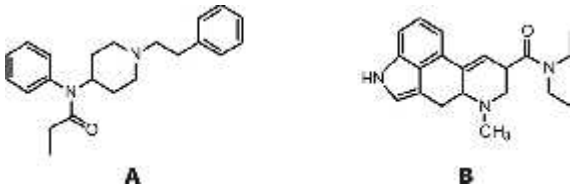


Figure 3. Molecular structures of (A) fentanyl and (B) LSD-25 (19-22).

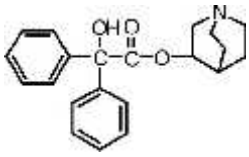


Figure 4. Molecular structure of BZ (23).

after exposure. As defined by the US Department of Defense (DoD), these agents are known to cause temporary psychobehavioural impairments (19). Fentanyl, lysergic acid diethylamide (LSD-25), and 3-quinuclidinyl benzilate (BZ). are among the common incapacitating agents.

Fentanyl (Figure 3A), also chemically known as N-phenethyl-4-(n-proprionylanilino). piperidine or N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl] propanamide, is an opioid with an immediate onset of analgesic effect. It is considered the most potent painkiller available to date, with potencies up 10,000× relative to morphine (20). Fentanyl was mainly developed as an anesthetic but alternative use as an incapacitating agent was imminent at exposures higher than therapeutic dose (20). Side effects include euphoria and respiratory depression causing sedation and immobilization. Although its use as an illicit drug has been regulated, it is not listed in the CWC schedules enacted in 1993, hence bearing the danger of being used as a warfare agent (20, 21). Mostly disseminated as aerosol, fentanyl pose more threat as an inhalation hazard with pharmacodynamic onset between 10 to 90 seconds and the effects lasting for few hours.

LSD-25 (Figure 3B). is usually referred to as "mind-altering" drug or a "phsychedelic", an extremely powerful behavior-modifying compound. This chemical agent is known to induce an overload of perplexing and imaginative thoughts and fears, rendering the victims fully incapacitated (19, 21). LSD-25 (or simply LSD). is a white crystalline, odorless, tasteless and a water-soluble compound. It is also chemically known as 9,10-didehydro-*N*,*N*-diethyl-6-methyl-ergoline-8-β-carboxamide. The effective dose of LSD was assumed to be 100 µg/kg but effects are manifested in as little as 25 µg. One study has seen effects on volunteers that were administered a 0.5 µg/kg oral dose of LSD in as little as 30 minutes with symptoms persisting for 4–8 hours (22).

BZ (Figure 4), a code name designated by NATO(6), is an extremely potent incapacitant. It is an environmentally persistent, odorless, white crystalline powder that can be disseminated as an aerosol(23). The main route of exposure is by inhalation but it can also be delivered intravenously and orally (11, 24). It is derived from belladonna, a poisonous plant in the nightshade family whose foliage and berries contain toxic tropane alkaloids (25, 26). Belladona is one of the oldest source of pharmaceuticals and anticholinergics like atropine (25). Like all anticholinergics, BZ inhibits the parasympathetic nerve impulses by binding to the muscarinic nerve cell receptors, competitively blocking the neurotransmitter acetylcholine. This significantly affects the central and peripheral autonomic nervous system, causing involuntary muscle movements and loss in coordination, cessation in perspiration and mucus production, and increase in temperature. Increase in heart rate, pupil dilation, flushing, vomiting, nausea and hyperthermia are few of the peripheral effects. Central nervous system effects include restlessness, agitation, confusion, cognitive dysfunction, changes in perception and mood, and lapses in attention. Mild delirium and hallucinations were also reported at exposures to higher dose. The lethal concentration of BZ vapor or aerosol to cause death in 50% of the exposed population (LCt_{50}). was reported to be 3,800–40,000 mg·min/m^3 (6). Inhalation experiments conducted by Ketchum and colleagues reported that regardless of the route of exposure to BZ, the exposed subjects would exert parasympatholytic effects (27-29). The reported ID_{50}, the dose that will incapacitate 50% of the population, was approximately 6.2 µg/kg (23, 28). A summary of the physical properties and toxicity of incapacitating agents is presented in (Table 2). (20-22, 30, 31)

3.3. Blood agents

Blood agents are cyanide-containing, toxic gaseous chemicals that are readily absorbed into the bloodstream via inhalation. These agents interfere with cell respiration, blocking oxygen uptake and transfer from the blood (11). Cyanide poisoning evidently produces red skin due to the blood circulating through the capillary beds

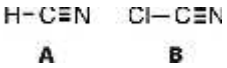


Figure 5. Molecular structures of blood agents (A) hydrogen cyanide (AC) and (B) cyanogen chloride (CK) (11, 25, 32).

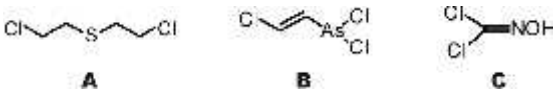


Figure 6. Molecular structures of vesicants A) mustard (HD), B) lewisite (L), and C) phosgene oxime (CX) (21, 25).

without unloading oxygen (8). Ultimately, the agents poison and proliferate systematically causing the body to suffocate and asphyxiate (11, 25, 32). Examples of blood agents are hydrogen cyanide (AC). and cyanogen chloride (CK). (Figure 5). AC is a colorless-to-yellowish brown liquid at room temperature but is highly volatile. It is also known as formonitrile, hydrocyanic acid or prussic acid (11, 33). The main route of physiological entry is by inhalation of vapor, although it can easily be absorbed via skin contact of the liquid or aerosol forms. CK, also known as chlorine cyanide or chlorocyan, is a colorless liquid that is denser than water and whose vapor causes irritation in the eyes, nasal, and other mucous membrane passages. Initial effects are similar to RCA exposure, but at exposure to higher concentrations, the nervous system can quickly shut down and paralyze. Immediate exposure to cyanide gas causes headache, nausea, weakness, hyperventilation, vertigo, anxiety and agitation. Within 30 seconds of exposure, loss of consciousness will occur slowly, progressing to apnea within 3–5 minutes. Violent seizures and cessation in cardiac activity, due to loss in respiration controls, at 5 to 8 minutes post-exposure will follow, and eventually, death (21, 34, 35). In case studies, rapid death from AC occurred with a dose as low as 0.7 mg/kg. An LCt_{50} of 524 ppm was also determined for a 10-minute exposure by inhalation, an LD_{50} for oral ingestion was 1.52 mg/kg, and an LD_{50} for dermal exposure was 100 mg/kg (33). Antidote administration is possible as the effects develop more slowly at lower concentrations of cyanide gas.

3.4. Vesicants

Vesicants, also known as blister agents, are chemicals that generally affect the skin and tissues causing burns or blisters upon contact. Though these agents are not usually considered lethal unless exposure occurs at high doses, excruciating pain is felt almost immediately after contact. The common agents under this category include mustards, lewisite and phosgene oxime. Mustard agents, first developed in the 1800s, caused the greatest number of non-lethal casualties in WWI (35). Crude mustard (H). is composed of approximately seventy percent 2,2'-dichlorodiethyl sulfide and thirty percent of a mixture of other sulfur compounds (25). Mustard gas (Figure 6A). is also known by the following names: sulfur mustard, S-mustard, HS, distilled mustard or HD, H, Kampstoffe, Lost, S-Lost, Schwefel-Lost, Y, Yellow Cross, yellow cross liquid, and Yperite (36, 37). It is a colorless-to-amber oily liquid whose name was coined from the taste or smell similar to onion, garlic or mustard (25, 37). Mustard is toxic to the skin, eyes and respiratory system. It is extremely poisonous with an LD_{50} of seven grams per person, and exposure to as little as one gram via inhalation can cause death within 30 minutes (20, 25). Immediate effects in skin may surface within two minutes but the pain due to systemic exposure, such as weakening of the immune system and clinical tissue effects, will take hours, in some cases up to a day, to commence (25, 34). Initial symptoms manifest as reddening of the skin and blisters may form depending on the dose exposure (11). Mustard agent is especially attractive for military weaponization due to the following reasons: high potency and prolonged effects, causes delayed and irreversible injury, persistence in the environment, difficult to decontaminate, penetrates respiratory masks and protective clothing, and easy and inexpensive to mass-produce (38).

Lewisite (*b*-chlorovinyldichloroarsine). is an oily, colorless, arsenic-containing compound sometimes referred to as Lyvizit or agent L (Figure 6B). It is less persistent compared to mustard but is equally toxic and causes pain upon skin contact within 12 seconds. (25). While mustard exposure effects are felt within hours, lewisite effects occur within seconds to minutes after exposure and produces immediate pain. The LD_{50} for lewisite was reported to be at 30 mg/kg, which is much higher compared to mustard, but the blistering effects of both agents were very similar. Eye contact with both mustard and lewisite causes inflammation, conjunctivitis, keratitis and eventual loss of vision. Respiratory tract injury is imminent depending on the duration and dose of exposure.

While mustards and lewisite induce boils or blisters, phosgene oxime forms a wheal in the affected site. Phosgene oxime (Figure 6C), also known as CX or dichloroform oxime, belongs to a class of CWA called urticants or nettle gases, which are compounds with penetrating odors and can intensely irritate skin, eyes and other mucous membranes (21, 25, 38). It is a colorless, crystalline solid that can be disseminated as a thermal fog (32). Like mustard agent, CX is attractive as a weapon of destruction due to its ability to penetrate rubber and other types of protective clothing. CX causes immediate symptoms of intense pain similar to a bee sting, severe itching and hives. These symptoms slowly progress to form a wheal and produces necrosis at the contact site (21). Eye exposure will cause keratitis, conjunctivitis, pulmonary edema and thrombosis at lethal amounts. Systemic effects are long lasting and the lethal dose is estimated to be in the range of 30 mg/kg (38).

3.5. Choking agents

Choking agents, also referred to as respiratory agents, mainly target the respiratory tract, particularly the nose, throat, and more importantly, the lungs. Upon inhalation, these agents damage the membranes between the air sac of lungs from the capillaries, causing difficulty in breathing and ultimately lung damage (8, 35). The chemicals essentially cause the lung membranes to fill with

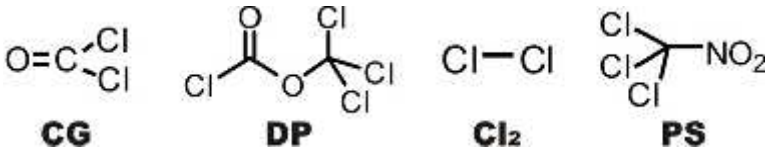


Figure 7. Molecular structures of choking agents phosgene (CG), diphosgene (DP), chlorine (Cl_2) and chloropicrin (PS) (11, 20, 21).

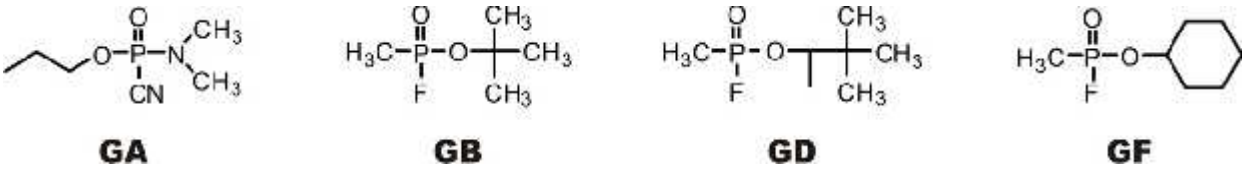


Figure 8. Molecular structures of the G-series nerve agents tabun (GA), sarin (GB), soman (GD) and cyclosarin (GF).

fluid, leading to pulmonary edema and respiratory failure (34). Examples of choking agents include phosgene, diphosgene, chlorine and chloropicrin. Phosgene and chlorine are good examples of "dual-use" chemicals, which are defined to have lawful and legitimate purposes but also bear the potential for improper and prohibited uses. For instance, phosgene is widely used in the chemical industry while chlorine has a variety of commercial applications (34-36).

Phosgene (CG), otherwise known as carbonyl dichloride (Figure 7). is the most toxic chemical among the respiratory agents (11). It is a colorless or white-to-pale yellow gas at room temperature and has been variably described to smell like mouldy hay or decaying fruit at low concentrations (11, 20, 21). Immediate signs of skin exposure are lesions similar to burns or frostbites, while symptoms of inhalation can range from watery eyes, scratchy throat, mild coughing, chest tightness and dyspnea to pulmonary edema (14). Exposure to concentrations of 3–4 ppm of CG can immediately cause milder symptoms such as eye irritation and chest tightness, while 30 ppm can cause significant lung damage, and 150 ppm will result in pulmonary edema. Diphosgene (DP), chemically known as trichloromethyl chloroformate (Figure 7), is a colorless oil with a freshly mown grass or green corn odor (20). It is more persistent and has a stronger lacrimating effect compared to CG. Upon exposure to DP, it is metabolized to CG, therefore the symptoms of exposure are similar to those of CG contact.

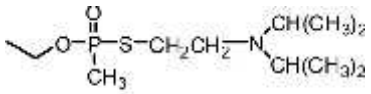
Chlorine gas (Cl_2). appears to be yellow-green in color and can be recognized by its pungent odor (Figure 7). Coughing, burning sensation of eyes, nose and throat, chest tightness, feelings of suffocation, nausea and vomiting are among the initial symptoms of exposure to chlorine. Prolonged exposure can cause difficulty in breathing, skin blisters and pulmonary edema.

Chloropicrin (PS). is a toxic chemical formed by the reaction of nitromethane with sodium hypochlorite. Also known as nitrochloroform (Figure 7), PS is a clear oily liquid with a known stinging and pungent odor. It is a severe respiratory irritant that causes nose and throat discomfort and vomiting upon inhalation (20). Skin contact can cause severe dermal irritations while eye exposure produces severe tearing, burning, pain and possibly corneal edema. Exposure to PS for 30 seconds at concentrations of 0.3–1.35 ppm will cause lacrimation. However, exposure at 1–3 ppm for less than 30 seconds will cause lung injury (11, 20).

3.6. Nerve agents

Nerve agents, chemically known as organophosphoric acid esters or organophosphorous compounds, inhibit the activity of acetylcholinesterase, the enzyme responsible for normal muscle and glandular function (39-42). Acetylcholine is the chemical transmitter acting at the junction where the nerve interfaces with the muscle (21). Normally, acetylcholinesterase halts the action of acetylcholine upon muscle contraction. Nerve agents block acetylcholinesterase, resulting in an accumulation of acetylcholine at the nerve endings. This affects the nerve impulses from the nervous system, causing involuntary and uncoordinated muscle movement (41). Nerve agents have been classified into two types: the G series and the V series agents. The G-series are organophosphate-esters containing fluorine or cyanide while the V series contain sulfur (11, 20). The well-known nerve agents are tabun (GA), sarin (GB), soman (GD). and VX. There are other V agents that have been produced such as VE, VG, VM and Vx gas, but in significantly lesser amounts.

First synthesized in the early 1930s in Germany, G series agents (Figure 8). are non-persistent, vapor hazards. These agents can disperse faster in a wider area of contamination and the main route of entry is via inhalation. GA is known chemically as *o*-ethyl *N*,*N*-dimethylphosphoroamidocyanidate (Figure 8). It is a colorless-to-brown liquid with a fruity smell if produced in a less pure form (11). GB, which was later developed by Germany and known as *o*-isopropyl methylphosphonofluoridate, is a colorless liquid with no odor in its purest form (11, 20). GD, chemically known as *o*-1,2,2-trimethylpropyl methylphosphonofluoridate, is a



VX

Figure 9. Molecular structure of VX (11, 32).

colorless liquid regarded as the most poisonous of the G-agents due to its quick effects in the central nervous system (20).

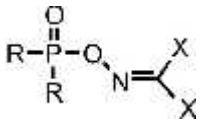


Figure 10. General chemical structure of NOVICHOK agents (32, 45).

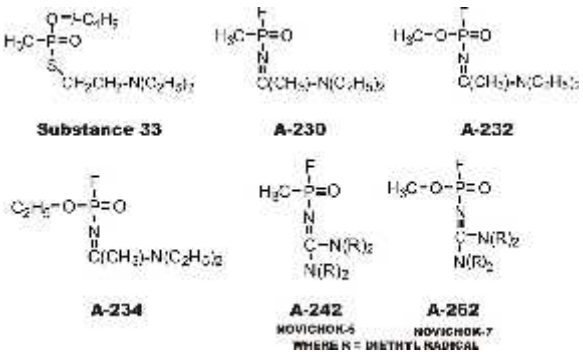


Figure 11. Molecular structures of the compounds believed to have been made in the "Foliant" program (45, 47, 48).

The V series agents, developed by British scientists around 1950, are highly persistent chemicals with very low vapor pressure (11, 32). VX (Figure 9), also called *o*-isobutyl *S*-2-(diisopropylamino). ethyl methylphosphonothiolate, is an amber-colored oily liquid that is much more toxic and fatal compared to any of the G-agents. Because of its persistence, VX poses a higher risk upon contact as oppose to an inhalation hazard. Drops of VX on any surface can persist for weeks to months and is known to be resistant to decontamination. It can be absorbed readily in porous materials like wood, fabric and plastic, therefore posing even more complications during decontamination (43). The onset of symptoms may be felt within one to ten minutes after exposure to VX. However, effects may be felt much later if exposure is at very low but continuous dose.

Exposure to any kind of nerve agent can occur through ingestion, inhalation of vapors, or cutaneous absorption. Effects can rapidly occur upon vapor inhalation, including immediate eye pressure sensation and redness, pupil constriction, increase in secretions, chest tightness, nasal congestion and wheezing, nausea, salivation and vomiting. Skin contact causes localized sweating and muscle twitching while ingestion causes diarrhea, vomiting, stomach cramps, involuntary urination and defecation, and muscle cramps. Severe exposure via inhalation results in restlessness, giddiness, anxiety, confusion, tremors, headaches, drowsiness, difficulty concentrating, memory impairment and respiratory failure, oftentimes leading to death (32, 42). Inhalation of vapour or aerosolized nerve agents is the most lethal way of exposure since agents immediately target the respiratory tract (11, 44). LCt_{50} was reported to be 70–100 mg·min/m^3 for GB, 150 mg·min/m^3 for GA, 40–60 mg·min/m^3 for GD and 50 mg·min/m^3 for VX (11, 20). Complete recovery is possible if exposure to nerve agents is mild to moderate.

3.7 Binary and non-traditional agents (NTA)

The term "binary" agent refers to two chemical entities, more often referred to as precursors that are synthesized individually for safe handling but rapidly react with each other upon combination to form the targeted lethal agent. Binary agents are easier to handle and transport at their precursor state but are extremely lethal once combined and upon impact. For instance, VX nerve gas can be dispersed as munition comprised of two precursors from separate compartments within a weapon. These compartments disintegrate once the weapon is deployed, allowing the reaction to occur and consequently producing VX. By the time VX is generated via the breakage of the precursor compartments, there is insufficient time to escape, even via a pre-planned route, since the chemical reactions are designed to occur very rapidly. Currently, there is no mandated distribution control of precursor chemicals, making these agents synthetically accessible. In addition, the precursors are constantly unmonitored by CWC authorities because these chemicals are classified as safe agents or "dual-purpose".

Non-traditional agents (NTAs). are a new class of binary agents whereby limited public or unclassified information is available. This class has been called "Novichok" agents (Figure 10), a Russian term for "newcomer"(32, 45). It is a series of novel chemicals, allegedly the most deadly nerve agents developed by the Soviet Union in the 1970s and 1980s (4). These chemicals are believed to be almost ten times more potent and deadlier than the G and V series nerve gases. (2, 4). These agents belong to the "4th generation chemical weapons", a category not covered and controlled by CWC (46). Information regarding the Novichok chemical weapons surfaced in the 1980s when two Russian chemists, Vil Mirzayanov and Lev Fedorov, openly published articles regarding the production of these agents as part of what the two chemists referred to as Russia's chemical weapons program or "Foliant" (32, 44, 45, 47, 48). These agents, whose list of codes names include Substance33, A-230, A-232, A-234, Novichok-5 and Novichok-7 (Figure 11), are believed ready to be deployed in their binary form as munitions (45, 47, 48). Since the precursors are benign, these agents are most likely excluded from the CWC watch list and therefore will not raise concern for authorities (2).

Current surveillance systems may fail if these detectors are not designed to detect the binary or "dual use"

Table 3. Summary of lethal chemical agents and toxicity data (11-49)

Agent		Code	Median Lethal Exposure LCt_{50} (mg-min/m^3 except where noted)	Physical Properties
Blood Agents	Hydrogen cyanide	AC	Varies with concentration: 2,000 mg-min/m^3 at 200 mg/m^3 4,500 mg-min/m^3 at 150 mg/m^3	Colorless liquid Highly volatile Rapid detoxification
	Cyanogen chloride	CK	11,000	Colorless liquid Highly volatile
Vesicants	Distilled mustard	HD	LD_{50}: 7 gm/person (estimate) 1,500 (respiratory) 10,000 (dermal)	Oily liquid; colorless gas 4-6 hour delay effects Very persistent
	Lewisite	L	LD_{50}: 30 mg/kg 1,400 respiratory 100,000 (dermal)	Colorless to brown liquid Rapid acting Less persistent than HD
	Phosgene Oxime	CX	3200 (estimated)	Solid (liquid above 39°C) Rapid Acting Persists for hours in soil
Choking Agents	Phosgene	CG	3,200	Colorless gas; volatile
Nerve Agents	Tabun	GA	400 (resting inhalation) LD_{50}: 1 to 1.5 mg/person (dermal dose)	Colorless to brown liquid Colorless gas Persistence ~ days
	Sarin	GB	100 (resting inhalataion) 70 (mildly active inhalation) 15,000 (dermal)	Colorless liquid Colorless gas Persistence < GA
	Soman	GD	70 (mildly active inhalation) 10,000 (dermal estimated)	Colorless liquid Colorless gas Persistence ~ days
	Fluoride-containing Organophosphate	GF	N/A for inhalation path LD_{50}: 16 to 400 µg/kg mice	Colorless liquid Colorless gas Persistence ~ days
	Standard V-agent	VX	100 (resting inhalation) 6 to 360 (dermal-clothed)	Amber Oily liquid Persistence ~ weeks to months
Binary nerve agents	Binary nerve agents	GB2 VX2	Similar to GB Similar to VX	Similar to GB Similar to VX

chemicals (49). It has also been reported that these compounds were designed to infiltrate current protective equipments, which ultimately can prove to be fatal, especially to the emergency first responders. A summary of toxicity data for all lethal chemical agents, including binary agents, is presented in (Table 3).

4. COUNTERMEASURES, MANAGEMENT AND TREATMENT

4.1. Learning from experience

Chemical weapons were introduced during World War I (WWI). with the release of chlorine, phosgene, mustard gas and other toxic agents by the Germans. The first types of nerve agents synthesized in Germany were also released during the war via aerial bombs and spray containers (44, 50-52). Germany continued to produce and research new chemicals intended to be used as warfare agents before and during World War II. Other countries also initiated independent chemical weapons program after WWI, including Britain, France, the Soviet Union, Japan and United States. The agents were stockpiled as weapons to be utilized offensively in case of an attack, or so it was believed. The United States and Soviet Union have produced and stockpiled the largest amount of chemical weapons during the cold war (2, 4, 10, 53, 54). Tens of thousand tons of these chemical agents are currently still being destroyed by both countries as part of the CWC treaty that entered into force in 1997, with the 2012 deadline for complete elimination of these agents approaching fast (2, 53).

The chemical capabilities of Iraq were clearly demonstrated in its attack against the Kurdish civilians and Iranian military personnel during the Iran-Iraq war (36, 50-52). It was learned and confirmed that mustard gas and nerve agent tabun were used, consistent with the wounds, injuries and symptoms of victims (51, 55). Substantial stocks of mustard agents, sarin, cyclosarin, tabun and VX were also found stored in several "dual-use" chemical facilities producing legitimate commercial products in Iraq. Even more disturbing was the fact that the nerve agents were stockpiled in their binary forms that are legitimately excluded from the CWC list. It was also found that the facilities have the capability to produce these nerve agents in massive amounts, then loaded into artillery weapons in virtually short amount of time (51)

A chemical terrorism attack made famous in the mid-1990s was led by the Aum Shinrikyo cult (2, 4, 32, 49). The group released sarin gas in Matsumoto, Japan on June, 1994 and in a Tokyo subway system on March, 1995. The dissemination methods were considered rudimentary, i.e., punctured trash bags around the subway station, but both events still killed almost 20 and injured over 1,000 civilians. The most recent events that are familiar to many are the outlines of the Oklahoma City bombing, the Sept 11, 2001 attacks, and the anthrax incidents in 2001 (56). All these cases illustrate the definite presence of chemical weapons proliferation threat not only in the US but also abroad. Intense domestic security has since focused on ensuring that the vulnerability of the US to such attacks is now minimal.

Table 4. Summary of response activities in the event of chemical warfare release (56)

Assess the risks	Use rapid chemical detection and identification techniques to determine the causative chemical agent Recruit specialist aid for definitive identification of agent With initial response initiated, activate more detailed assessments regarding dose-response relationships, exposure assessment and risk characterizations
Manage risks	Protect responders Contamination control – establish "hot zone" scene control to limit contamination spread; conduct immediate decontamination onsite, and decontamination of all persons leaving the "hot zone" Conduct casualty triage Ensure medical care and evacuation of casualties Conduct definitive decontamination of the site
Monitor all activities	Decide whether local and national resources are adequate, and whether international assistance should be sought Continuously monitor the residual hazard level on the site, and adjust response activities as needed Repeat the risk-assessment/management process as required Implement follow-up activities (long term-injuries and rehabilitation)
Communicate the risks	Implement a risk communication program for the affected population that conveys information and instruction as needed

As the years passed since the initial use of CWAs in WWI, intensive knowledge about different chemical agents and dissemination techniques has been advanced. Fortunately or unfortunately, depending on how you look at it, this expertise was acquired not only by the scientific experts but also by rouge individuals and organizations who intend to deploy the chemical agents for terrorism. Difficult to perceive and almost impossible to avoid, chemical threat is insidious, and preparedness is the most important countermeasure anybody could make. These terrorist events and experiences provide a definitive reason for any country to devise a defensive plan in case chemical agents are advertently released.

4.2. Preparedness and response

A CWA attack is discernable, perhaps becoming a real threat that cannot be completely eliminated. Stockpiling and proliferation of CWAs is definitely a concern for the military planners, intelligence officers and government systems. There must be a formulated general response strategy and plan in the event of a CWA release. These protective measures need to originate from government officials and military personnel as well as civilians. From the perspective of a concerned citizen, there is always a question whether the medical, military and civilian communities are ready when CWAs are released. More importantly, countermeasures, medical protocol and incident management procedures currently in place by the defense officials have, thankfully, not yet been tested in a real-life CWA event. The domestic preparedness program was established in 1996 by the US Department of Defense (DoD). with the main objective of helping enhance the federal, state and local capabilities to respond to Nuclear, Biological and Chemical terrorism threats (57). Preparedness is simply a careful, advanced planning on protocols necessary to manage an incident. In light of the recent sarin release in Tokyo, and the fact that hundreds of "dual-use" chemicals are legitimately produced and not strictly controlled, CWAs are easy to produce. It is not a question of "IF" a CWA attack will happen but rather a matter of "WHEN" it is going happen. Having a preparedness program in place (Table 4). (56), with risk management, medical treatment and decontamination procedures established, can be a good defense in itself.

A preparedness program for a CWA attack requires the acquisition of surveillance and detection systems, equipments and supplies for protection, appropriate triage identification protocols and medical treatment, decontamination procedures and public health plans for contamination control. There is also a need for for the emergency first responders and medical service personnel to undergo specialized training specific to a chemical agent release. The question "What levels of insanity do we have to prepare for?" posted by the Nobel Laureate, Joshua Lederberg,(58). serves as a reminder that having a preparedness program for the purpose of safety can never be deemed wrong.

The first step in any preparedness program is the threat analysis. This involves experts from the military, intelligence, law enforcement, first responders, and medical and scientific field, to coordinate in identifying possible threats and response scenarios. Although fairly broad in intensity, this will help identify chemical agents of biggest concern, highly targeted areas or population, and intended delivery methods for a type of chemical agent. Knowing the exact nature of the next chemical attack may be close to impossible, but the liaison between different sectors of government will help outline a means of prioritizing an approach for preparedness protocol. With the probability of an incident calculated, as well as functional needs and solutions stemming from the national guideline,(59). every locality can devise a protocol that best suits their ability to manage the incident (56). Once the different scenarios have been identified, the corresponding responses and resources that are necessary to alleviate consequences of chemical warfare attack can be summarized. Support from international allies, if needed, may be sought. Government and international agencies like the World Health Organization (WHO). have a list of sources for such kind of assistance (60)

Response before any overt release of chemical agents is the ideal scenario of a well-prepared community or country. Table 4 summarizes a guideline from WHO of the response activities needed to be in place in the event of an intentional chemical agent release. The primary step requires acquisition of equipments capable of broadcasting an advanced warning of an apparent chemical agent threat. It would be ideal if the devices can identify the chemical agent(s). released in real time although a detect-to-warn system would be sufficient. This calls for the much-needed technology or equipment that could detect, warn and identify the chemical warfare agent in real time. If a warning alarm is received, the first step in the protocol has to be the analysis of any available information. A confirmation that the warning is a deliberate chemical agent release, and not a false alarm, will be crucial in the following steps of the response protocol. Search procedure

to identify the source and the nature of the hazard being confronted is necessary. Safety of any civilians in the exposed area is top priority, so either a confinement of the contaminated area or evacuation procedures have to be initiated.

Once the release of chemical agent is confirmed, neutralization of the situation and risk reduction must be initiated. This entails enlisting personnel specially trained for the particular type of CWA release, including decontamination procedures, mass casualty management and large-scale distribution of medications or vaccines (56). Emergency responders skillfully trained in handling chemical warfare agents have to be present on site to manage the decontamination. These responders need to have sufficient training in first aid and treatment, identification of triage and public health plans in case of mass casualty. Appropriate training for all the staff in the first line of help will prove to be crucial under the circumstances of CWA release.

Decontamination procedures, mass casualty management and large scale distribution of medications or vaccines need to be addressed in the training of first responder and medical personnel (56). Once a specific area of attack has been identified, decontamination needs to be immediately administered before the casualties can be further treated at any hospital. It needs to be ensured that not one more person becomes affected, including medical personnel. In any kind of emergency treatment, a decontamination area and protocol at all hospitals has to be in place. This will be the only way to manage the casualties and avoid further contamination in the hospital or treatment facilities. Decontamination usually begins with a thorough washing of the eyes, skin and other exposed areas with water and a dilute bleach solution (35, 61). In addition to transporting the victims away from the contaminated area, decontamination will halt additional exposure time to the victims. The responders are also expected to be decontaminated before evacuating out of the "hot zone" (*i.e.*, contaminated area). to prevent contamination of the treatment facilities (35, 54).

Liquid agent exposure in skin or clothing and other garments may be more complicated. A skin agent decontamination kit may be used such as M291 or M2581A1. The M291 kit contains a decontaminant resin Ambargard WE-555,(62). while the M258A1 kit contains two packets of decontaminating wipes consisting of a mixture of hydroxyethane, phenol, ammonia, sodium hydroxide, chloramines B, zinc chloride and water (62). A deployable decontamination equipment is also necessary on site to avoid secondary contamination of emergency transport and medical receiving facilities. Training of skilled individuals in this specialized area and emergency management protocols will serve the best efforts in responding to CWA incidents.

Laboratory facilities that can quickly identify the chemical agent released also need to be trained for the public health preparedness protocols. Although state-of-the-art diagnostic systems for identification of chemical warfare agents may not yet be available, the best possible system currently available will be at least be sufficient. Specialized training of civilian medical personnel is also crucial in cases of chemical agent illnesses. These personnel must quickly diagnose the first signs of deliberate chemical poisoning and address the treatment necessary. It was noted that after the sarin attacks in Japan, the quick recognition of the medical personnel of the symptoms of nerve agent exposure was the first indication of a chemical release incident. (56). At the very least, identification of the category of CWA used will dictate the necessary antidotes or treatment needed to counteract the effects of poisoning even before confirming the exact identity of chemical agents. Failure of local health facilities and personnel to diagnose a deliberate chemical warfare release in a timely manner can cause a wider contamination area and possibly increase the number of casualties.

Every locality must have adequate devices and supplies, as well as protocols in handling of hazardous materials. The preparedness program requires the acquisition of personal protective equipment (PPE). for the protection of emergency first responders and medical personnel. First responders should be equipped and trained to effectively utilize PPEs, such as respirators and full body protection or clothing resistant to the suspected chemical agent released. These PPEs must be designed to allow a wide range of mobility to ensure that responders are able to perform their duties – decontamination and management of casualties – and not become casualties themselves. The performance of PPEs plays a major role in managing deliberate chemical warfare attack. Moreover, the relay of events following the CWA release will greatly depend on how the first responders execute responsibilities in the early critical moments of the chemical hazard incident: neutralizing the disaster area and evacuating as many exposed and affected civilians as possible.

It is recommended that, if available, antidotes, vaccines, antibiotics and PPEs should be stockpiled in a high-risk area. Sources of these supplies also need to be identified, with the standard procedure of rapidly obtaining emergency supply in case of mass casualty. One can argue that such preparation may be a burden in cost, especially in budget-limited countries. At the very least, selective countermeasure like stocking of PPE for first responders and medical personnel, and of antidotes for high-risk CWA has to be considered. Furthermore, it is essential to reiterate that equipments for advanced, real-time detection of chemical agents are important aspects of any CW defense and preparedness program.

Preparing a communications package and public information is challenging in any preparedness program. Protocols for the dissemination of information to the public in cases of deliberate chemical warfare attacks should always be ready. Any communication package poses risks of public panic and chaos depending upon the content and timing, so each item has to be carefully considered and clearly addressed before release. Panic of the general population will be counterproductive and dangerous if the communication packages are not well constructed (56, 63).

Table 5. Indicator of Chemical Agent Release (21, 56, 64)

Epidemiological Features	High number of patients almost simultaneously with similar symptoms: respiratory, ocular, cutaneous or neurological, nausea, headache, eye irritation, difficulty breathing, convulsions or sudden death
	Patients coming in from one locality
	Pattern of symptoms clearly evident

Table 6. Common chemical agents and symptoms of exposure (5)

Group	Chemical agents	Symptoms of exposure
Nerve agents	GA (tabun), GB (sarin), GD (soman), GF (cyclosarin) and VX	Runny nose, tightness of chest, dimness of vision and miosis, difficulty breathing, drooling and excessive sweating, nausea/vomiting, involuntary defecation and urination, twitching, jerking and staggering, headache, confusion, drowsiness, confulsions, coma. And eventually, death. Death is caused by respiratory arrest, as all respiratory muscles contract
Blister agents	HD (mustard), L (lewisite), CX (phosgene oxime)	Redness of skin that develops into blisters or wheal
Choking agents	CG (Phosgene)	Sneezing, chest pain, chest tightness, choking, difficulty breathing
Blood agents	AC (hydrogen cyanide), CK (cyanogens chloride)	Convulsions, rapid deep breathing and bradycardia followed by shallow breathing and eventual cessation of breathing. CK has choking and strong irritation effects

The response capabilities of any local region or a country can only be validated during simulated training sessions. At that point, the preparedness protocols can be critically evaluated and areas in need of improvement can be identified. Past events, as discussed in the section *Learning from Experience*, can be analyzed thoroughly to be able to execute a preparedness plan. Although every experience may be different, a general outline can be drawn from each incident in order to have the best strategy of handling future attacks by the first responders. Effective measures for coordination of government agencies in providing emergency care – command, control and communication – can help reduce casualties. The response mechanism will certainly involve a multidisciplinary group of highly-specialized individuals. Therefore, the preparedness and response protocols would require a properly identified person in command at every level of responsibility.

4.3. Medical management

By definition, medical management "consists of procedures for optimized medical care which includes the following: triage, basic survival treatment, decontamination, emergency forward treatment, evacuation, and continuing protection of chemical agent casualties" (21). For triage, prioritization of casualties will be Immediate, Delayed, Minimal and Expectant (64). This is a common practice in any medical facility but is especially important in case of mass casualty, where the goal is to save as many lives as possible. A treatment for basic survival needs to be administered before, or at the very least, while decontamination is happening whenever possible. (Table 5). shows a summary of features or indicators of a chemical agent release based on the number of patients and similarities in symptoms.

Each type of chemical agent causes a variety of symptoms (Table 6). (5). There needs to be a clear understanding of the inherent effects from exposure to these chemical agents in order to effectively implement a medical countermeasure. Hence, complications arise from failure to identify the class of chemical agent used in the attack. Protocols may be different in a scenario where civilians were targeted versus the military personnel in a battlefield. Medical treatment may also be limited by the resources available in the public health system and in the field. One aspect is certain though: if the emergency first responders, medical care providers, and military medical personnel received proper training to determine if CW contact has occurred, an immediate and proper medical treatment can be administered so that casualties will be greatly reduced.

Blood agent exposure has been shown to be reversed by antidotes like amyl or sodium nitrite combined with sodium thiosulfate (35, 65). Because cyanide is metabolized fairly quickly, prompt treatment is essential to the recovery of the victims. Ventilation with oxygen can assist victims with difficulty or shallow breathing. Anticonvulsants are also administered to avoid or aid with convulsions. Common effects of exposure to liquid and gaseous mustards during WWI range from minor tissue damages to pneumonia that led to death. Effects of a blistering agent like mustard can be local or systemic depending on the dose and duration of exposure. Immediate effects like skin lesions are apparent with respiratory adverse effects due to continuous exposure or if immediate decontamination of the affected area was not administered. The only medical treatment administered is symptomatic treatment with antibiotics to prevent other infections (21, 36). Victims of choking agents showing of tightness in the chest and coughing are kept rested as lung damage can be exacerbated by strenuous activities. Supplemental oxygen may be required on victims with shallow breathing (21, 66). Exposure to a more lethal dose of respiratory agents will likely cause a fluid build-up in the lungs. Corticosteroids have been administered and recommended under this circumstance although proof of benefits remains uncertain (67).

Treatment of nerve agent poisoning will require immediate decontamination and respiratory support. Regardless of the type of nerve agent and dose exposure, paralysis of diaphragm and other respiratory muscle is inevitable. The last step of treatment would be the antidote therapy like cholinolytics, oximes and diazepam. Atropin, which blocks the action of excess acetylcholine, is a well-known cholinolytic that has been used as an antidote for years. Although the initial antidote administration is extremely necessary for any nerve agent exposure and poisoning, continued treatment will require medical expertise because side effects can be lethal if not monitored correctly. Oximes like pralidoxime chloride (2-PAM). and obidoxime (toxogonin). can help restore cholinesterase

activity. 2-PAM is capable of reversing the actions of the nerve agents (35). However, side effects from these medications can be difficult to manage if the dosage of poisoning is not known. Oximes are also not very effective for soman poisoning since this nerve agent quickly and irreversibly reacts to acetylcholinesterase (68). For mass casualty management, atropine and 2-PAM or obidoxime can be administered quickly in the form of first aid auto-injectors (68). Diazepam is administered to help reduce severe convulsions that can cause brain damage (35). Both atropine and 2-PAM are available in the antidote kit called MARK 1, while diazepam is produced as CANA, a kit often used by US troops during the Gulf War (35).

There are no known phrophylactic antidotes for chemical threat agent exposure (41). It has been reported that the administration of physostigmine or pyridostigmine chloride can offer some protection agains soman. However, success rates have been questionable and side effects have not been identified (35, 65, 68). There is only a hypothesis that physostigmine or pyridostigmine chloride can help prevent permanent binding of nerve agents to the nervous system. It can supplement the effects of the antidotes atropine and 2-PAM upon administration, and can offer protection or delay in the effects of soman. The US Army Medical Research Institute of Chemical Defense also developed the Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA). – a chemical resistant topical cream – to complement the protective clothing used by military soldiers (35, 69). SERPACWA is a 50:50 mixture of perfluoroalkylpolyether (PFPE, CAS # 69991-67-9). and polytetrafluoroethyelene (PTFE, CAS # 9002-84-0), that serves as a physical barrier against chemical warfare agents. Clinical and non-clinical studies have shown that a thin layer of SERPACWA can reduce or delay dermal exposure to chemical agents (70).

The question remains: are we, as civilians and a community, prepared in the event of a CWA release? Joint Chemical and Biological Defense Program (CBDP). set forth by the US DoD clearly outlined all measures being enacted to protect the nation and its allies from emerging threats posed by CWAs and other weapons of mass destruction (WMD)(71, 72). The US DoD designated programs for defense training, equipment acquisition, education, and preparedness to ensure proper operations are executed successfully in the event of attack (73-75). Recently, medical and physical science and technology researchers have outlined accomplishments relevant to chemical defense (73). Medical pretreatments, therapeutic strategies and chemical prophylaxes are constantly being improved to protect individual health and reduce injuries or deaths in the event of CWA release (76). Progress is reassuring enough to conclude that the defense capabilities of the United States in the best possible position (73, 77). In addition, there is a continuous flow in therapeutic strategies that intend to help reduce the probability of long-term health effects on the victims (73, 76). For instance, new approaches to treat organophosphate exposure have been investigated, including atropine replacement, anti-seizure medications, catalytic bioscavenger, neuroprotectant, and improved cholinesterase reactivator (73, 77). Studies on the mechanism of action of NTA in central nervous systems, animal models and potential therapeutic approaches have been completed. In addition, new candidate oximes which are centrally active against the traditional CWAs and NTAs have been developed (73, 77). Furthermore, a chemical diagnostics assay for simultaneous identification and quantification of several nerve agent metabolites in biological fluids has been developed (73). These accomplishments definitely position the medical community ahead of the preparedness plan for CWA defense. Current status of research and development helped streamline our defense capabilities in readiness for current and future WMD challenges (58). Moreover, it must be remembered that no matter how good any preparedness plan may be, there may be unforeseen technical difficulties associated with the aftermath of an actual CWA release.

5. CHEMICAL AGENT DETECTION METHODS

5.1. General requirements

As mentioned in earlier sections of this review, early detection of released CWA is vital to minimize casualties. Cutting-edge technologies that meet the criteria of affordability, portability, real-time response and identification capability factors are most desirable. Detectors currently in the market and under product development vary in the advantages, and hence in disadvantages as well. However, no product can encompass all the requirements needed to detect ALL or just about ANY kind of CWA. In other words, there is no individual chemical detector that can possibly satisfy ALL the requirements.

The applicability of the chemical detector is dependent on the performance characteristics of the equipment and the type of chemical agent it can detect. Of the several factors needed to be considered when selecting a detector, the most important criteria may be the specific application and operational need (78). A technique that works for one type of chemical agent may not be applicable for another depending on the mechanism of detection. Numerous technologies exist mainly for detection of liquid samples on surfaces, while others are tailored to detect vapors or aerosols. Knowing the chemical agent to be detected offers the advantage of being able to design a system specific for the application need. In the following sections, several detection techniques, technologies and commercially available devices will be discussed. Detector selection will rely on performance and detection capability (78). Sensitivity, selectivity, limit-of-detection (LOD), response time, false-alarm rate, quantitative analysis and agent identification capability fall under detection capabilities. Performance capabilities include size and portability, power or battery requirements, ease of in-field calibration, time needed to warm-up and power-up, and environmental resistance.

Selectivity and sensitivity have always been the major aspects of detector requirements. Selectivity is a term that refers to the capability of a detector to respond to specific target analyte in a pool of samples. Sensitivity is

Table 7. Estimated Allowable Exposure Levels (AEL) of Chemical Agents (8)

Chemical Agents		Lethal exposure limit estimates	Other established exposure limit estimates
Nerve agents	GA	13	0.0001
	GB	3	0.0001
	GD	2	0.00003
	GF	N/A	N/A
	VX	3	0.00001
Choking agent	CG	100	0.002
Blood agents	AC	150	0.003[1]
	CK	400	0.008[1]
Vesicants[2]	HD, L	~50	0.003
	CX	100	0.003[1]

[1]Limited operational temperature and humidity range [2] Representative exposure limits

the ability to detect and discriminate the target analyte at the lowest concentration possible. There needs to be a striking balance between sensitivity and selectivity since current detectors that are highly selective may not always be highly sensitive and vice versa. The most challenging aspect for chemical agent identification is the capability to effectively extract the necessary information on a chemical agent in the presence of other environmental interferents.

Limit of detection (LOD). is the lowest concentration of chemical agent that a detector can identify with a high degree of confidence. The government has published exposure level guidelines for various chemical agents that may be used in warfare (79). Nerve, vesicant and blood agents were reported to have acute toxicities of 10^{-3}g/person while emerging and non-traditional agents can be toxic at 10^{-10}g/person (80). Ideally, chemical detectors should be able to offer LOD levels that are significantly lower than the exposure guideline. In addition, advanced warning alarms will allow evacuations to occur and medical countermeasures to be administered on time. (Table 7). provides the allowable exposure level (AEL). guideline generally used by the US government in evaluating chemical detection technologies(8). Detectors that have the sensitivity to detect near the AEL levels of chemical agents are the most ideal. However, only non-portable systems currently have this capability (8, 78).

Other factors that need to be carefully considered are the false alarm rates and response time. Real-time monitoring and detection will usually offer the best advantage especially in a possible target-prone area. False alarms, regardless of either a false-positive or false-negative, are also a real consideration in choosing an ideal chemical detector. False-positive alarms happen when a detector responds to feedback that is arising from the background. A secondary mechanism to confirm analyte identity will help avoid these types of false events. False-negative occurs when the detector fails to respond even in the presence of a real chemical agent threat. False negative events are even more dangerous than false positive events since lack of first-responder activity can result in a disastrous situation. Performance factors like environmental resistance, calibration, set-up and warm-up requirements, device weight, portability, and battery life play major roles depending on the application need for specific detectors in consideration. For instance, the Joint Program Executive Office for Chemical and Biological Detection (JPEO-CBD). sector of the US government has outlined the war fighter needs for chemical detection devices (81). In addition to the requirement for confident detection performance – sensitivity, selectivity, zero false alarms – it is best for the detectors to be small or hand-held, with simple robust designs, easy to operate and capable of remote or stand-off detection. In an ideal world, a "tricorder" – a pointing device made famous in a science fiction movie– than can identify an unknown agent within seconds is the perfect detector (80). Though a tricorder is a very high standard for an ideal chemical agent detector, it is only the aim of the following sections to review the advancements in the development of analytical techniques used to detect CWAs. The review does not intend to exhaustively discuss all chemical warfare detectors, currently available off-the shelf or detectors and technologies under research and development. Only a general survey of analytical techniques and chemical agent detectors for a variety of military, security and defense applications will be discussed. An overview of detector features and applications relevant to chemical agents will also be summarized. The intent is to be able to provide a guideline in selecting the best options for long term monitoring, real-time detection, and identification of CWAs.

5.2. Remote or standoff monitoring

One of the main criteria for chemical agent surveillance and monitoring is "remote" or "standoff" detection. This refers to the ability of a detector to spot, evaluate and identify an agent at a distance. Sampling occurs at the point of interest but the detection device is operated from another or remote location. This should allow warning signal to be transmitted to the receiving end after a chemical agent presence is detected. Ideally, information on the nature of the incoming threat should accessible in real time from the detectors. In turn, proper countermeasures can be taken to ensure the safety of the general public.

5.2.1. Infrared spectroscopy

Infrared technology is the most common analytical technique employed in stand-off CWA detection. Detectors that employ IR spectroscopy technique are generally used only to determine if a CA is present in a sample rather than identifying them (7, 82, 83). The IR region in the electromagnetic spectrum, ranging from 0.78 to 1000 microns (μm)(82, 84), can be divided into the near, mid and far IR regions. The regions are as follows: near IR ranges from 0.78–2.5 μm (12800–400 cm^{-1}); mid IR ranges from 2.5–50 μm (4000–200 cm^{-1}). and far IR extends from 50–1000 μm (200–10 cm^{-1}). (82). The detection

Figure 12. M21 RSCAAL (88, 89).

Figure 13. RAPID (90).

Figure 14. MIRAN SapphIRe (82, 85, 93).

application wavelengths are usually in the mid range of 2.5–15 µm (4000–670 cm^{-1}). (82, 85, 86). In IR spectroscopy, radiation is transmitted through the analytical sample and the instrument measures the amount of light absorbed at a specific wavelength. During IR transmission, some radiations are absorbed by the sample while others are transmitted. For every chemical group, such as the phosphorous-oxygen bond in nerve agents, this motif creates a unique molecular fingerprint. Every sample of different chemical group will absorb at specific wavelengths, and the concentration is proportional to the intensity of IR absorption (83, 84, 87). For instance, it has been determined that the characteristic wavelengths for GA, GB and HD are 9.7, 9.9 and 13.9 µm, respectively (82, 85). IR-based detectors offer the advantage of high sensitivity, fast detection and response, low LOD, non-destructive sample analysis and no sample preparation is required (82, 83). However, major disadvantages of these detectors are the cost, complexity and size of instrumentation (82, 84). In addition, current detectors based on IR techniques are sensitive to vibration and therefore limits their portability as handheld devices (82-84).

IR spectroscopy is utilized in several chemical agent detection techniques, including photoacoustic IR, fourier transform (FTIR), forward-looking IR (FLIR). and filter-based IR (7). The first fielded chemical detection standoff device used by the military is the M21 Remote Sensing Chemical Agent Alarm known as RSCAAL (Figure 12). (88, 89). It is based on passive FTIR detection technology, which allows monitoring and sampling of unknown chemical agent vapor clouds at a "safe" distance. M21 is capable of detecting nerve and blister agent clouds as remotely as five kilometers away (7, 8, 88). It has to be noted that for M21 to work effectively, it needs be stationary rather than mobile, and detection is easily obstructed by dust, rain and snow (88)

Bruker manufactures Remote Air Pollution Infrared Detector (RAPID). based on FTIR technology (Figure 13). (90). It is a robust stand-off detector that monitors, detects and identifies CWAs such as GA, GB, GD, HD and L, as well as other TICs in the low parts-per-million (ppm). range, at distances of up to 5 kilometers (91). These systems can be mounted to moving vehicles, naval vessels or aircrafts, without sacrificing performance. RAPID incorporates Bruker's RockSolid^{TM} flex-pivot interferometer, allowing the detector to operate in static or moving conditions. It is also known to be capable of assessing cloud positioning using its integrated cloud positioning software (CPS). (92).

MIRAN SapphIRe Portable Ambient Air Analyser (Figure 14), manufactured by Thermo Electron Corporation, is a portable single beam IR spectrophotometer (82, 85, 93). The device is capable of detecting GA, GB and HD at levels that are at least an order of magnitude higher than AEL and IDLH levels (85). Field testing of MIRAN SapphIRe at ECBC concluded the instrument is very sensitive to humidity in addition to background interference (82). Overall, MIRAN SaphIRe was found to have very low sensitivity for CWA detection in the field.

The AN/KAS-1/1A Chemical Warfare Directional Detector (CWDD). (Figure 15), an FLIR system, is a passive IR imaging sensor currently used mainly by the US Navy (94). It can detect and identify nerve agents in a sky background, periods of low visibility or night surveillance (95). It has not been evaluated in

Figure 15. AN/KAS-1/1A (93).

Figure 16. HazMatID™ (95, 96).

terms of its response with respect to changes in temperature, relative humidity or interferences (82).

HazMat ID (Figure 16). was originally developed by SensIR technologies (Danbury, CT). but is now widely distributed by Smiths Detection (Watford, UK). (96). It is a lightweight, rugged and waterproof detector that is simple and easy to use, and operable in extreme temperatures and humidities (97). One unique feature of the system is its ability to be operated wirelessly or remotely (98). An assessment of IR-based detectors is summarized in (Table 8). (82, 91)

5.2.2 Raman spectroscopy

Raman spectroscopy is an analytical technique that provides information on vibrational, rotational and other low-frequency molecular motions that can be used to identify and quantify samples (99). The technique is based on illumination of the sample with a monochromatic laser source and detecting the scattered light as a function of wavelength (82, 100). Raman effects occur when the photons of the source are absorbed by the sample and re-emitted at a frequency different than that of the monochromatic frequency. The inelastic scattering of the monochromatic excitation source, defined as the change in frequency of the incident light source, occurs upon contact with a sample. The wavelength of the re-emitted scattered light is shifted to a different wavelength compared to the monochromatic incident light source. Such variation in wavelength allows the assessment of species based on their "fingerprint" Raman signatures. (101).

Similar to IR technology, Raman spectroscopy allows a non-destructive method of CWA analysis. Irradiation of the sample in a transparent glass or container is possible, therefore minimizing the environmental exposure of the chemical agent. Advantages are high specificity, low signal-to-noise ratio and no sample preparation is required (82). However, one major disadvantage of this technology is its incapability of detecting and identifying agents in non-transparent munitions (82, 84). In addition, Raman technology has been reported to produce false-positive and false-negative events, and is weak at detecting low-concentration chemical agents in a mixture of background materials (102).

RepondeR RCI (Figure 17), manufactured by Smiths Detections is a field-portable Raman spectrometer used mainly for the detection and identification of nerve and blister agents (103). AhuraFD, developed by Thermo Scientific and formerly marketed as Ahura Scientific First Defender (Figure 18), is a handheld, lightweight and rugged Raman spectrometer that identifies CWAs and select TICs (104, 105). A side-by-side comparison of currently fielded detectors based on Raman technology is summarized in (Table 9).

5.3. Point detectors

Detectors that physically sample a chemical agent cloud are usually referred as "point" detectors (84). The detection device is capable of continuous sampling in a single location or can be operated by personnel on-site with more specific training.

Figure 17. RespondeR RCI (102, 103).

Figure 18. FirstDefender Systems (103-105).

5.3.1. Colorimetric

Enzymatic detection technique of CWA is considered to be the least sophisticated and least expensive method of detection (84). The technique utilizes a chemical detection paper composed of a dye mixture in the target chemical agents and pH indicators. The detection paper is designed to exhibit a visible color change according to the type of agent detected. This technique is primarily qualitative, lacks specificity and is prone to errors because it can react to interferents in the sample matrix (8, 84). The most common colorimetric detectors are available in the form of papers or detection tubes (106)

Commercially available products include the M8 (Figure 19A). and M9 (Figure 19B). chemical papers used by the military. M8 paper is an off-white paper that produces a color change upon contact with liquid agents. It changes to deep red when exposed to mustard agents, scarlet with lewisite, yellow for GB, and dark green with VX (107). M8 paper can be used as a confirmatory test as it changes color within 30 seconds of exposure to chemical agents (7). However, it is not capable of detecting vapors and extremely small droplets of agents. Both M8 and M9 papers react to the same agents and are usually employed in side-by-side testing. The latter reacts faster to chemical agents and can be attached to clothing or moving vehicles up to a speed of 30 mi/h. Another chemical agent detector, the M256A1 sampler kit (Figure 19C), was later developed to integrate the detection chemistry of the M8 and M9 papers. The reagents are contained in glass ampoules which are broken and allowed to react to vapor samples contaminated with the chemical agents (107). Change from a colorless solution to bluish purple, for instance, signals the presence of mustard. M256A1 is more sensitive than either M8 or M9 papers, and can detect nerve gas, mustard and cyanide. It is known to detect nerve gas concentrations as low as 0.005 mg/m^3, mustard agents at 0.02 mg/m^3 and cyanides at 11 mg/m^3 (7). M8, M9 and M256A1 detectors have been demonstrated to be prone to false-positive results and M256A1 can sometimes require up to 15 minutes to detect chemical agents. The only advantage noted was the fact that these techniques have not exhibited false-negative results in actual events (7).

Colorimetric tubes (Figure 20), such as those available from Draeger and RAE systems, use enzymatic techniques to identify CWAs. A hand pump draws a sample into a specific tube and the concentration of the substance is read from the tube. Such process is a simple and inexpensive way of detecting and identifying a chemical agent. For these reasons, it is used extensively in civilian response units despite a number of disadvantages. Available are 160 substance-specific reagent tubes identifying different agents. For each agent, a different tube must be used. Efficient use of this system demands knowledge of which CWA is likely to be present in a given environment. A tube for each possible CA must be used for thorough detection. Draegar has made this process simpler by offering a chip measurement system (CMS). analyzer. The analyzer incorporates an optical system for analyzing the color reaction, a flow controller, a pump system, and ten capillaries, each capable of detecting a unique agent. As long as the proper chip is inserted, ten agents can be detected simultaneously and measured accurately within 20 seconds (7). (Table 10). summarizes the sensitivity and response of colorimetric detectors.

Agentase™ CAD-Kit (Figure 21). provides surface, solid and liquid sampling to emergency first responders with the advantage of simple, immediate response. It can detect nerve, blood and blister agents as well as specific toxic industrial chemicals. It requires minimal training, no calibration is needed, offers resistance to common environmental interference, and is robust enough to function under various environmental conditions (108).

5.3.2. Ion mobility spectrometry

Ion mobility spectrometry (IMS). is an analytical technique that uses an ionization source such as the radioactive Nickel 63 or Americium 241 (7, 109). The gaseous sample is drawn into the reaction chamber, then

Table 8. Comparison of available IR-based detectors (82, 90, 91)

Criteria	M21 RSCAAL	RAPID	MIRAN SaphIRe	AN/KAS-1/1A	HazMat ID
Detected Agents	Nerve, HD, L vapor	GA, GB, GD, HD and L	Nerve and blister agents		Nerve agents, vesicants
Response Times	Line of sight dependent	10-60 secs	~ 18 seconds		Less than 20 seconds
Limits of Detection	Nerve agents: 90 mg/m^3 L:500 mg/m^3 HD: 2000 mg/m^3(132)	GA at 0.013 ppm GB at 0.009 ppm GD at 0.012 ppm HD at 0.02 99m L at 0.03 ppm	GA at 1.3 mg/m^3 GB at 0.83 mg/m^3 HD at 2.54 mg/m^3(93)		
Portability and Weight	Two man portable Detector is 23.6 kg Tripod is 6.8 kg (133)	40 lbs	Standoff <12.5 kg(93)	Man portable < 12 kg	Man portable < 10.5 kg

Table 9. Comparison of available raman detectors

Criteria	RespondeR RCI	FirstDefender
Detected Agents	Common chemicals, WMDs	CA's, toxic chemicals, explosives, narcotics
Response Times	>30s, <60sec	< 15 sec
Limits of Detection	Not provided	Not provided
Portability and Weight	6 lbs	kg

Table 10. Comparison of detector sensitivity and response

Criteria	M8 / M9	M256 kit	Detector Tubes
Detected Agents	GB, VX, HD, L	HD, L	GB, VX, HD, L
Response Times	< 20 sec	13 mins	1-3 mins sometimes variable
Limits of Detection	100 µ drops	Nerve: 0.005 mg/m^3 Mustard: 0.02 mg/m^3 L: 2 mg/m^3 CX: 2 mg/m^3 AC & CK: 3 mg/m^3	
Portability and Weight	Handheld	Handheld	Handheld

Figure 19. Colorimetric paper detectors A) M8, B) M9 and C) M256A1 kit (7, 106).

Figure 20. Colorimetric detector tubes (106-108).

Figure 21. Agentase CAD-Kit (107, 108).

Figure 22. CAM Smiths Detection (108-115).

Figure 23. APD2000 (108-114)

ionized by the source and passed towards the ion detector. The vapor phase chemical agents form ion clusters upon contact with their parent ions, which are then identified by their unique transit duration from the reaction chamber drift to the detector (8). Each chemical agent responds differently to the source since the ion clusters formed are proportional to the size, shape and weight of the agent. IMS is one of the commonly used technologies in chemical agent detection, offering a wide range of applications. Primarily due to its simple principle and very fast detection capability, IMS is integrated with other analytical techniques, such as mass spectrometry, that are employed by military and security personnel (82). IMS detectors are pretty rugged in design, lightweight, require very little consumables, have low power consumption, inexpensive to manufacture and can be easily miniaturized for field use (82, 83, 110). IMS technique has gained a high rate of interest in its use by the military and first responders for the detection of very low levels of CWAs and other toxic vapors in the field. It is known for its low limits of detection, usually in the parts-per-billion (ppb). to parts-per-million (ppm). range, with only a few seconds of response time (83). However, a number of disadvantages for IMS detectors are notably poor selectivity and false alarms (110, 111). These detectors were also shown to be very much affected by fluctuations in temperature, pressure and humidity, where failure in CWA identification occurred or detection signals were difficult to interpret (112). Aspiration IMS is a fairly new application that has been used to detect chemical agents like VX and soman degradation products (113, 114)

Among the chemical detectors utilizing the IMS technique are M80 and M90, Chemical Agent Monitor (CAM), Improved Chemical Agent Monitor (ICAM), Advanced Portable Detection (APD). 2000, and Sabre FR. M80 and M90 are hand-held devices manufactured by a Finnish company, of which a limited amount of information is available. CAM (Figure 22). is a handheld device, manufactured by Smiths Detection, to detect nerve, blister and blood agents. ICAM is a hand-held device that can also be attached to mobile vehicles to continuously monitor nerve agent concentrations. It has been widely used during the Gulf War but was found to report erroneous responses in closed spaces and in heavily smoked areas (7). Response time for CAM and ICAM generally takes 10 to 60 seconds. APD200 (Figure 23). and Sabre FR (Figure 24), both are manufactured by Smiths Detection, are commercially available and used by HAZMAT teams and first responders. APD2000 detects nerve agents, blister agents, and other hazardous materials such as mace and pepper spray. Sabre FR is used mainly by first responders to detect trace particles of explosives, drugs such as cocaine and heroin, and chemical warfare agents.

There are also standalone detectors that use IMS technology such as Automatic Chemical Agent Alarm (ACAA), formerly known as M8A1. This system continuously monitors the area of concern for hazardous vapors and aerosols of nerve agents, and emits an alarm within 1–2 minutes of chemical agent contact. It can detect nerve and blister agents as low as 0.1 mg/m^3 (7). Others have reported that M8A1 or ACAA can detect GA, GB,

Table 11. Assessment of available IMS detectors (82)

Criteria	CAM	APD2000	SABRE	GID-3 (M22 ACADA)	RAID
Detected Agents	Blood, blister, choking and nerve agents	GA, GB, GD, VX, HD, L, pepper spray and mace	GA. GB. GD, GF, VX, Vesicants, TICs, drugs and explosives	GA, GB, GD, VX, HD, L	GA, GB, GD, GF, VX, HD, HN, L
Limits of Detection	LOD in line with or exceed the NATO requirements	V agents – 4 ppb; G agents – 15 ppb; H – 300 ppb; L – 200 ppb			Low ppb up to several ppm
Portability and Weight	Hand-held < 2 kg	Hand-held < 3 kg	Hand-held < 3.5 kg	Vehicle mounted < 7 kg	Hand-held < 3 kg

Figure 24. SABRE4000 (108-114).

Figure 25. M22 ACADA (GID-3) (108-114).

Figure 26. RAID-M-100 (115).

and GD at 0.1–0.2 mg/m^3 and VX at 0.4 mg/m^3 (8). M8A1 has since been replaced with M22 automatic chemical agent detector alarm (ACADA). or GID-3 (Figure 25). M22, also based on IMS technology, is capable of detecting nerve and blister agents. It has been widely used during the Gulf War where its communications interface was found very useful. M22 can be fully automated upon integration with systems such as multipurpose integrated chemical agent detector (MICAD). Comparable to M22 and M8A1 is the Centurion II, manufactured by Smiths Detection. It is considered as a standalone IMS detector capable of detecting nerve and blister agents. Centurion II showed superior *non-response* to background and other interferences.

Bruker recently announced the production of Improved Point Detection System – Lifecycle Replacement (IPDS-LR), which is based on the RAID-S2 (Figure 26). technology for the detection of CWA and TICs (115). The system utilizes a high-performance IMS technology for trace vapor detection of hazardous agents. The device is designed to be operational under a variety of environmental conditions and for significantly longer periods. It may also be mounted in a stationary position or in vehicles and naval vessels for mobile monitoring of CWAs (116). (Table 11). summarizes the assessment of available IMS detectors. (82).

5.3.3. Surface acoustic wave sensors

First reported in 1979, surface acoustic wave (SAW). sensors are the most selective detector systems (117). A SAW device consists of a piezoelectric crystal that continuously propagates an acoustic wave in the surface due to an applied electric field. The SAW sensor detects changes in the acoustic wave that travels along the piezoelectric plate that is usually made of quartz (83, 86). Detection of CWA by the SAW technology is based on the attenuation of the acoustic wave due to the interaction of the chemical agent or analyte with the surface of the piezoelectric crystal sensor (8). The sensor surface is coated with a polymer film chemically designed to specifically adsorb a target analyte. When the target chemical agent is adsorbed onto the surface of the piezoelectric material, changes in amplitude of the acoustic wave occurs, resulting in a positive identification of the agent.

Detection of CWA using SAW devices offers the advantage of good sensitivity, fast response, low cost manufacturing, and can be easily miniaturized (82, 118). SAW detectors should have very low false-alarm rate since the polymer coating of an SAW sensor is, in theory, designed to adsorb only very specific agents. In reality, however, the polymer coatings usually adsorb other types of agents (84). In addition, the polymer coatings are sensitive to environmental conditions and respond erratically when used outside its operating temperature and humidity range (118).

Table 12. Assessment of available SAW-based detectors (82, 120)

Criteria	SAW MINICAD	HAZMATCAD	JCAD	CW Sentry
Detected Agents	GA, GB, GD, HD	GA, GB, GD, GD, VX, HD, AC, CK, CG and TICs	GA, GB, GD, GD, VX, HD, L, AC, CK,	VX, GA, GB, GD, GF, HG, AC, CG
Response Times	60 sec analysis time	20-120 sec	10-90 seconds Concentration dependent	20 seconds
LOD	GA: 0.2 mg/m^3 GB: 0.5 mg/m^3 GD: 0.1 mg/m^3 HD: 1 mg/m^3	GD and HD: high sensitivity mode close to IDLH limits in up to 4 min	GA: 100 mg/m^3 GB: 30 mg/m^3 GD: 50 mg/m^3 within 12-13 sec HD: 40 mg/m^3 within 8 secs L: 300-10000 mg/m^3 within 15 sec	Nerve: 0.04-0.16 ppm Blister: 0.14 ppm Blood: 5 ppm
Portability and Weight	Light, handheld 0.5 kg including battery	0.65 kg	Handheld < 1 kg	Designed to be permanently installed 18.2 kg

Table 13. Assessment of available FPD (82, 124)

Criteria	AP2C	AP4C	MINICAMS
Agents Detected	G, V, and H agents	CWAs and 49 of the 58 chemicals on NATO's TIC list	Detects and alarms to all chemical warfare agents, precursors, stimulant materials and related industrial chemicals.
Response Times	< 2 sec	2 sec	3-10 min
Limits of Detection	GB – 10 µg/m^3 HD – 400 µg/m^3	G agents – 20 µg/m^3 HD – 600 µg/m^3 Liquid VX – 3 µg/m^3	GA & GB – 0.1 µg/m^3 GD – 0.03 µg/m^3 VX – 0.01 µg/m^3 Blister agents – 3 µg/m^3
Portability and weight	Handheld < 2.5 kg with battery and hydrogen storage device	Handheld < 2 kg with battery and hydrogen storage device	Portable 9 kg

Figure 27. SAW MiniCAD (118-120).

There are numerous SAW technology-based CWA detectors that are currently fielded. Detection limits as low as 0.01 mg/m^3 within 1–2 minutes have been reported for SAW detectors (80). Microsensor Systems, Inc. manufactures a handheld, portable, lightweight and battery-operated SAW array detector. It is commercially available as SAW MiniCAD mk II (Figure 27**).** and is commonly used by civilian first responders for CWA detection. Microsensor systems have demonstrated the capabilities of SAW MiniCAD mk II to detect nerve agents at 0.04 ppm in 20 seconds, and blister gas agents at 0.01 ppm in 120 seconds (119, 120). Other detectors are HAZMATCAD, ChemSentry 150C, CW Sentry Plus and Joint Chemical Agent Detector (JCAD). (Figure 28). An assessment of currently fielded SAW technology-based detectors is summarized in (Table 12). (82, 121)

5.3.4. Flame photometry

The next predominant technology in the field for CWA detection, following IMS, is flame photometry. More accurately called Flame Atomic Emission Spectrometry, this technology analyses the spectrum of a flame. Each excited CWA clusters generate unique light emission properties as the high energy clusters relax to the lower energy states (82, 83). Although Flame Photometry Detectors (FPDs). are currently fielded, more detectors are commonly found integrated with Gas Chromatography (GC). for routine lab analysis (7, 83, 122). A Flame Photometry device draws air samples into a reaction chamber via air pumps, samples are then incinerated in a hydrogen-rich flame, and any compounds present emit radiation of specific wavelengths. A spectrum that is unique to the atoms or compounds present in the sample serves as a fingerprint for a particular agent. FPDs utilize optical filters that allow only specific wavelengths of light to transmit. Optical filters specific for phosphorus and sulfur are used in CA detectors based on FPD technology since these are the key elements of nerve agents and distilled mustard (HD), respectively (84, 86, 122). Therefore, FPDs are not prone to interferences and are very specific and sensitive to phosphorus and sulfur atoms in the environment. FPDs have been reported to provide instantaneous detection of both phosphorus and sulfur atoms in the ppb and ppm range (122). Like any other analytical technique for CWA detection, FPD does not guarantee an all-in-one detection. One major disadvantage associated with this technology is its capability to detect compounds that only contain either phosphorus or sulfur. As such, regardless of its selectivity to nerve agents and mustard, it is prone to false positives to any other substance containing these elements. In addition, it can only indicate the presence of either phosphorus or sulfur in a sample (123). A precise identification of the unknown substance is not possible.

The Proengin AP2C (Figure 29)**,** a chemical detection that systems use the principles of flame spectrophotometry to detect nerve and blister agents at fixed locations. These detectors operate automatically, continuously and require a minimal monthly supply of 1.2 L of distilled water. AP2C*e* is an improved version of AP2C, which can be used in a more rugged environment

Figure 28. A) HAZMATCAD, B) JCAD and C) CW Sentry (118-121).

Figure 29. AP2C (124).

and flammable atmospheres. AP4C on the other hand has the added capability of detecting a wide range of TICs, which positively reported 49 out of the 58 TICs in the NATO list, and have very low false alarm rates (124).

A GC-FPD device commercially available from O.I Analytical (College Station, TX). is the MINICAMS (Figure 30). It can detect a wide array of CWAs and CWA vapors at sub-AEL levels, within a five-minute cycle (82, 83). (Table 13). presents a summary of assessment of performance of current FPD detectors (82, 125)

5.3.5. Photoionization detectors and electrochemical detectors

Photoionization detection (PID). is based on the ionization of gas vapors using ultraviolet (UV). light (82, 126). This highly sensitive technique allows detection of compounds at very low concentrations (ppb-ppm). Only certain CWAs that have ionization potentials lower than the UV light can be ionized and detected (127). However, PID systems have very limited specificity and are known to produce false alarms in unknown environments (82)

As defined by Taylor and Schultz, an electrochemical sensor "detects and measures changes caused by the interaction between the chemical agent and an electrical circuit" (8, 128). Fundamentally, the chemical agents are detected by its interaction with an electrode, exhibited by changes in the electrode potential. Although electrochemical detectors are known for their high selectivity, the technology generally suffers from low sensitivity. In addition, a number of fielded electrochemical detectors exhibit unpredictable behaviors when exposed to extreme environmental conditions (129)

An example of a handheld detector currently available utilizing the integrated PID and Electrochemical technology is SensorRAE Conditioning System by RAE Systems (Figure 31)(129). Numerous PID detectors are also available from RAE systems and Photovac (Figure 32 and Figure 33). Limited information is available on various RAE detectors and has not yet been evaluated in its field performance (82).

5.3.6. Carbon nanotube gas ionization sensors

An emerging technology in the CWA detection is the development of miniaturized carbon nanotube gas ionization sensors. These types of sensors have been known to be limited by sensitivity and highly responsive to environmental conditions leading to unpredictable responses. Improvements in sensitivity have been reported in more recently fabricated devices and sensors, providing the technology more advantages over the FPD and PIDtechniques (7). The Cyranose 320 manufactured by Smiths Detection is one example of currently fielded detector utilizing this technology (Figure 34).

6. SUMMARY AND PERSPECTIVE

The previous sections covered only a fraction of current analytical technologies utilized in the field of chemical detection. The roster of detection techniques is continuously expanding due to the volume of research in recent years. A great deal of attention has focused on developing arrays of chemical agent (CA). detectors or sensors (82, 83). This involves the integration of previously discussed detection technologies into a large array, enabling a more sensitive and selective approach. A device that is highly reliable in detection with fewer false alarms is the goal that is intended to be accomplished through side-by-side confirmation of results between the various detectors. Currently, there is no known "commercially available" or "fielded" sensor array technology device (82).

One field highly relevant to the development of detector array is nanotechnology. Requirements like integrated miniaturized detectors, disposable, have low power requirements, cost-effective, capable of unmanned operational deployment and networked to a central station

Table 14. Comparative Research and Development Status for Chemical Detection

	Fundamental Research	Applied Research	Prototype	Field Trials (Pre-commercialisation)	Deployed (Commercialised)	Mass Market
Conductive Polymers		•	•	•		
Field effect transistors		•	•			
Piezoelectric		•	•	•		
Surface acoustic		•	•	•	•	
Sensor arrays		•	•	•	•	
Optical Fibers		•	•	•	•	
Cantilevers			•	•		
Chemiresistor			•	•	•	
Chemicapacitors		•	•	•		
Spectroscopic method			•	•	•	•
Nanomaterials for detection		•	•	•		

Figure 30. MINICAMS (82-84).

Figure 31. SensorRAE (128, 129).

Figure 32. RAE systems A) ToxiRAE, B) MultiRAE and C) MiniRAE gas detectors (82).

all seem feasible in the field of nanotechnology (74, 82, 119, 130). Furthermore, detector stability in different environmental conditions provide another parameter that needs to be standardized in detector and sensor fabrications (130). Technologies enabled by nanomaterials that are currently being explored for sensor arrays include conductive polymers, semi-conductor cells, chemiresistors, piezoelectric sensors, field-effect transistors, optical fibers, cantilevers, chemicapacitors, SAW devices, spectroscopic methods, metal oxides and various nanomaterials for detection (119). These integrated sensing technologies are currently still at the research stage and (Table 14). summarizes the comparative research and development status for CWA detection as of 2009 (119). For the purpose of the comparative R&D status, the following definitions are given (119):

Fundamental research – preliminary research with no particular goals of commercialization

Applied research – research in academia and industry towards a specific application

Prototype – fundamental or applied research that has found market application

Field trials – currently field tested for commercialization

Deployed – technologies that have found early-stage market

Mass market – technologies that have been adapted by large population

Designing portable, miniaturized, field deployable devices capable of remote and real-time detection, with high sensitivity and selectivity, is still a major challenge. There is no single device that currently meets ALL the requirements of chemical agent detection (119, 131). Technologies discussed in this review have their own advantages and disadvantages, and each one clearly presents a considerable room for improvement. Current detection capability is still somewhat limited, which warrants the need for even further research into the development of new technologies aimed at building

Figure 33. Photovac PID detector (82-83).

Figure 34. Cyranose 320 (108-114).

detectors of highest sensitivity and selectivity possible for targeted chemical agents. Currently, the biggest challenge in the field of CA sensing is the integration of technologies to achieve the needed selectivity and sensitivity. Reliability of existing detectors continues to require improvement, especially with the goal of reducing the frequency of false events.

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Abbreviations and acronyms: AC: Hydrogen Cyanide, ACADA: Automatic Chemical Agent Detector and Alarm, AEL: Acceptable exposure limit, APD: Advanced Portable chemical agent Detector, BZ: 3-quinuclidinyl benzilate, CA: Chemical Agent, CAM: Chemical Agent Monitor, CAs: Chemical Agents, CBDP: Chemical and Biological Defense Program, CBRN: Chemical, Biological, Radioactive and Nuclear, CG: Phosgene, CK: Cyanogen Chloride, CN: ortho-chloroacetophenone, CR: dibenzo (b,f)-1,4-oxazepine, CS: ortho-Chlorobenzylidene-malononitrile, CWAs: Chemical Warfare Agents, CX: Phosgene oxime, DM: diphenylaminearsine, DoD: Department of Defense, DP: Domestic Preparedness, DP: Diphosgene, ECBC: Edgewood Chemical Biological Center, FID: Flame Ionisation Detection, FIDs: Flame Ionisation Detectors, FLIR: Forward Looking Infrared Spectroscopy, FPD: Flame Photometric detection, FPDs: Flame Photometric detectors, FTIR: Fourier Transform Infrared Spectroscopy, GA: Tabun, GB: Sarin, GC: Gas Chromatograph, GD: Soman, GF: Cyclosarin, HAZMAT: Hazardous Materials, HD: Sulfur Mustard, ICAM: Improved Chemical Agent Detector, ICt50: Incapacitating concentration and time of a toxic substance required to kill 50% of an exposed population, IDLH: Immediate Danger to Life and Health, IMS: Ion Mobility Spectrometry, IPDS-LR: Improved Point Detection System-Lifecycle Replacement, IR: Infrared, JCAD: Joint Chemical Agent Detector, JPEO-CBD: Joint Program Executive Office for Chemical and Biological Detection, JSLSCAD: Joint Service Lightweight Standoff Chemical Agent Detector, L: Lewisite , LCt50: Lethal concentration and time of a toxic substance required to kill 50% of an exposed population, LD50: Median lethal dose of a toxic substance required to kill 50% of an exposed population, LOD: Limit of Detection, LSD-25: lysergic acid diethylamide, mg/m3: Milligram per cubic metre, MICAD: multipurpose integrated chemical agent detector, NATO: North Atlantic Treaty Organisation, NIOSH: National Institutes of Occupational Safety and Health , NTA: Non-Tradional Agent, OC: Oleoresin capsicum, OSHA: Occupational Safety and Health Organization, PID: Photo Ionisation Detection, PIDs: Photo Ionisation Detectors, Ppb: Parts per billion, PPE: Personal Protective Equipment, ppm: Parts per million , PS: chloropicrin, RADS: Reactive airway disease syndrome, RAID: Rapid Alarm and Identification Device, RAID-M: Rapid Alarm and Identification Device - Monitor, RCAs: Riot-control Agents, RSCAAL: Remote Sensing Chemical Agent Alarm, SAW: Surface Acoustic Wave, SERPACWA: Skin Exposure Reduction Paste Against Chemical Warfare Agents, TICs: Toxic Industrial Chemicals, UV: Ultraviolet, WHO: World Health Organization, WMD: Weapons of Mass Destruction, WWI: World War I, WWII: World War 2, µm: microns

Key Words: Review, Chemical warfare agents**,** detection, chemical detectors, Non-traditional agents, NTA, binary Chemicals, Nerve Agents, Riot-Control Agents, RCA, Incapacitating Agents, Vesicants, Blood Agents, Blistering Agents, Review

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