The Threat of Mid-Spectrum Chemical Warfare Agents

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TICs = toxic industrial chemicals

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Abstract

There is a spectrum of several threat agents, ranging from nerve agents and mustard agents to natural substances, such as biotoxins and new, synthetic, bioactive molecules produced by the chemical industry, to the classical biological warfare agents. The new, emerging threat agents are biotoxins produced by animals, plants, fungi, and bacteria. Examples of such biotoxins are botulinum toxin, tetanus toxin, and ricin. Several bioactive molecules produced by the pharmaceutical industry can be even more toxic than are the classical chemical warfare agents. Such new agents, like the biotoxins and bioregulators, often are called mid-spectrum agents. The threat to humans from agents developed by modern chemical synthesis and by genetic engineering also must be considered, since such agents may be more toxic or more effective in causing death or incapacitation than classical warfare agents. By developing effective medical protection and treatment against the most likely chemical and mid-spectrum threat agents, the effects of such agents in a war scenario or following a terrorist attack can be reduced.

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Introduction

"Mid-spectrum agents" is a term used to describe a part of the classical, chemical, and biological spectrum of threat agents. There is some public confusion about the similarities and differences between chemical and biological weapons and biotoxin weapons; these weapons have very different characteristics. Chemical warfare agents, in most cases, are man-made chemicals, and usually are super-toxic chemicals that can be dispersed as a gas, aerosol, vapor, liquid, or as agents adsorbed to particles to become a powder. Biological warfare agents include microbes such as bacteria, viruses, and rickettsia. It is convenient to regard chemical and biological weapons as part of a spectrum of materials. These weapons range from classical chemical warfare agents such as nerve agents, mustard agents, and cyanide through toxic industrial chemicals (pharmaceuticals and pesticides) to human neuro-hormones (such as bioregulators) and plant, animal, bacterial, and fungal toxins as well as to traditional biological warfare agents such as anthrax and plague (Figure 1).[1] Some of these warfare agents are extremely toxic, and therefore, lethal, while others have incapacitating effects on humans. The Chemical Weapons Convention contains provisions covering classical chemical weapons and naturally occurring toxins.[2] The Biological and Toxin Weapons Convention prohibits the use of toxins in warfare as well as traditional and modified micro-organisms.[3]

Thousands of toxic substances are known to mankind, but only some of

these agents are deemed suitable for use in chemical warfare. Since 1900, about 70 different chemicals have been used or stockpiled as chemical warfare agents. Toxic chemicals are any chemical that can cause death, temporary incapacitation, or permanent harm to humans or animals. Chemical weapons are defined as toxic chemicals and their precursors, munitions and devices, and any equipment specifically designed for use directly in connection with such weapons. The best-known chemical warfare agents are the nerve agents (inhibit acetylcholin-esterase), the mustard agents (alkylates, DNA, RNA, proteins, etc.), cyanides (block the enzyme cytochrome oxidase in mitochondria), lewisites (inhibits many different enzymes), phosgenes (causes pulmonary oedema), chlorines (causes pulmonary oedema), tear gases (cause irritation by activation of sensory receptors), and herbicides (disrupt food supplies and defoliate vegetation) (Table 1). For complete definitions, consult the Chemical Weapons Convention, 1993.[2]

The term "mid-spectrum agents" is used to describe that part of the chemical and biological spectrum of threat agents that covers bioregulators and biotoxins. Examples of such agents are the neurotransmitters substance P and neurokinin A, the biotoxins saxitoxin, ricin, and botulinum, and many other agents (Table 2).[4,5] The primary target of these substances is the nervous system and many have a very high neuro-toxicity. They are among the most toxic substances known to mankind. Knowledge of their chemical structure and toxicity has increased during the last decades, particularly as a result of the pharmaceutical industry's interest in the use of such agents for the medical treatment of several disorders.

Over the last decade, it has been feared that terrorists might be tempted to acquire and use such weapons against innocent civilians. The major reasons for the production and use of such weapons are manifold. First, chemical weapons and toxin weapons are cost-effective, particularly when utilized against concentrated forces or populations. Second, they may be used at lower levels of concentration to hamper military forces using protective equipment, or with an aim to cause panic and disorder among civilians.

This article reviews the threat of mid-spectrum chemical warfare agents and the role of international prohibition in the prevention of their use by terrorists (Table 3).

Mid-Spectrum Chemical Warfare Agents

Biotoxins

Biotoxins are biologically active agents produced from terrestrial or marine animals, plants, fungi, or bacteria. Generally speaking, there are two groups of biotoxins: (1) protein toxins consisting of long, folded chains of amino acids; and (2) non-protein toxins, which generally are small molecules with a complex chemical structure.[6] Several biotoxins have been identified as possible warfare agents because of their toxicity, specificity, and physiochemical properties. It is the physiochemical characteristics of the biotoxins that determine whether they are suitable for use as warfare agents (for a review on novel toxins and bioregulators, see Canadian Report).[7] Exposure to such agents would be associated with inhalation or contamination of water or food supplies.

The most potent biotoxins are neurotoxins such as botulinum toxin and tetanus toxin, but there also are others such as staphylococcal enterotoxin. Different bacteria produce each of these biotoxins. Botulinum toxin is the most toxic agent known to man and is a very potent neurotoxin, which blocks the release of acetylcholine from cholinergic nerves of the human nervous system. The lethal dose for humans of such toxins is in the sub-microgram range, which is many times lower (more toxic) than is the range of dosage for nerve agents such as sarin, soman, and VX. There presently are no available automatic detection devices for detecting the presence of biotoxins on the battlefield or for operational use by military medical services. Nor is there any specific medical treatment available against such intoxications, which thereby increases the potential threat from such agents as possible new weapons of warfare.

Following Iraq's invasion of Kuwait in 1990 and during the United Nations Special Commission's inspections in Iraq from 1991 to 1998, it became clear that Iraq had had the largest and most sophisticated chemical and biological weapons program in the developing world.[8-10] In addition to the production of several nerve agents, mustard agents, and biological warfare agents, Iraq also produced and weaponized several highly potent toxins such as botulinum toxin and aflatoxin. The Iraqi aflatoxin was produced by growing the fungal mold Aspergillus in 5-liter glass flasks. According to the above-mentioned reports, Iraqi scientists also performed several scientific studies using many different toxins including studies on the toxic effects of aflatoxin both in isolation and in mixtures with other chemicals. Aflatoxin was placed in rockets, bombs, and scud missile warheads for field trials at several test ranges in Iraq. In total, about 2,200 liters of concentrated aflatoxin was produced by Iraq.

Aflatoxin is well-absorbed orally, but exposure to skin results in a slow absorption. Aflatoxin does not cause an immediate effect in humans, but might form reactive DNA adducts, and thereby, cause cancer at some time following exposure. Therefore, aflatoxin poisoning is difficult to diagnose clinically early after exposure. Thus, the question is, why did Iraq produce and fill aflatoxin into weapons in concentrated form or as a mixture of aflatoxin and other warfare agents? One plausible explanation for production of aflatoxin as a chemical warfare agent is the objective to exterminate sub-populations within a country by making use of the long-term effects of aflatoxin as a cancer-inducing weapon.

Bio-regulators

Bio-regulators are a group of agents consisting of proteins and peptides. Peptides are short fragments of proteins that are composed of amino acids. They are naturally occurring substances in the human nervous and hormonal systems. Bio-regulatory peptides usually are highly active biologically at low concentrations. Their normal range of activity is very broad and covers many living processes involving the nervous and hormonal systems such as systems controlling emotions, blood pressure, temperature control, fear, mood, sleep, consciousness, etc. The result of exposure to

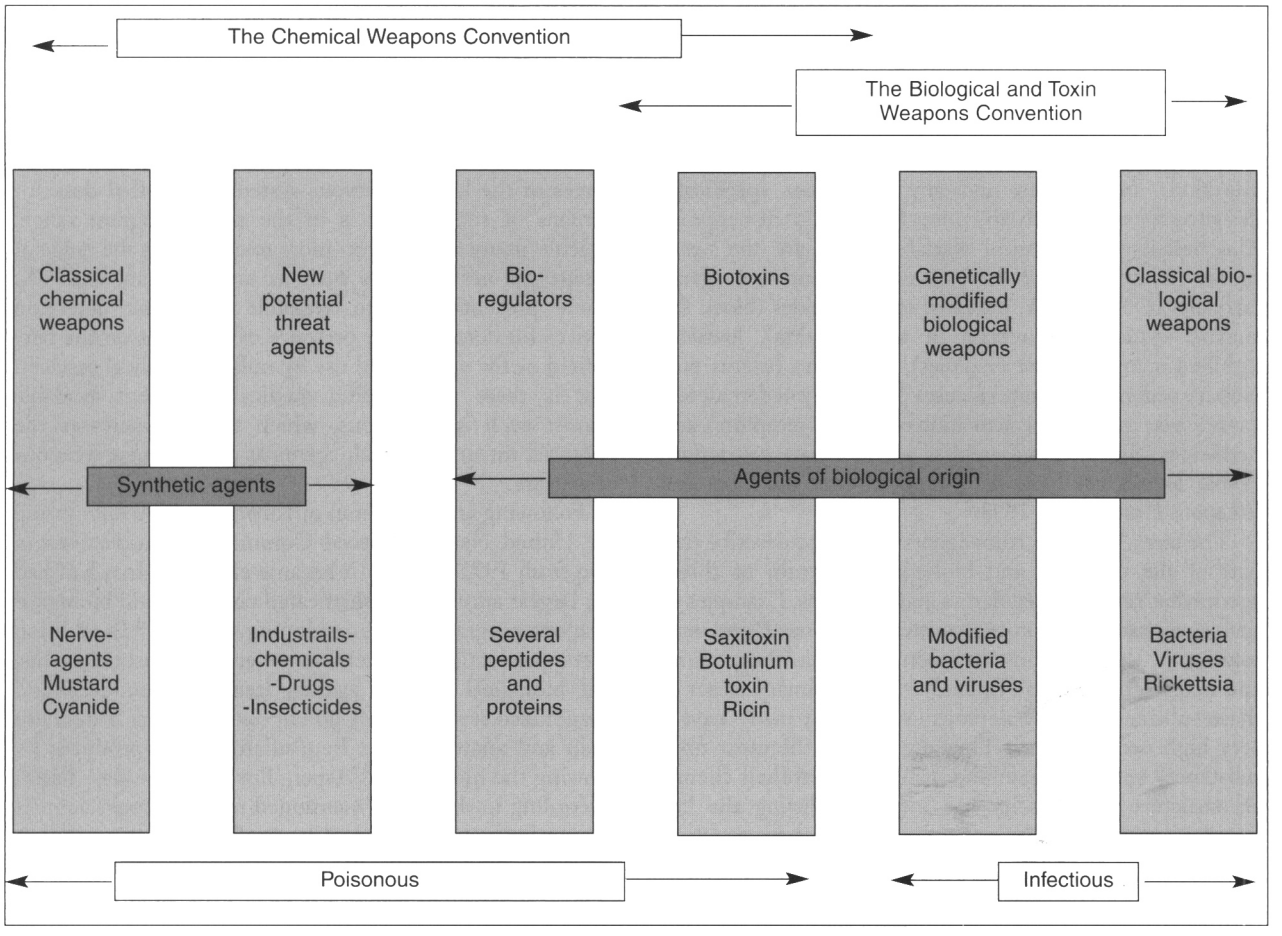

Figure 1—The chemical and biological spectrum of challenges

Nerve Agents
- Sarin (GB)
- Cyclosarin (GF)
- Soman (GD)
- Tabun (GA)
- VX

Blistering Agents
- Sulfur mustard (HD)
- Nitrogen mustard (HN)
- Lewisite (L)
- Phosgene oxime (CX)

Dyanide Agents
- Hydrogen cyanide (AC()
- Cyanogen chloride (CK)

Incapacitating Agents
- BZ
- LSD

Riot Control Agents
- CS
- CN
- CR
- Adamiste (DM

Herbicides
- Defoliants

Table 1—Typical examples of classical chemical weapons

such agents orally or by means of inhalation could have serious consequences including fatigue, fear, physical and mental incapacitation, and ultimately death.[7] Therefore, these agents not only should be considered as lethal agents, but also as non-lethal, incapacitating agents. Examples of relevant bio-regulators are endogenous opioids, which induce analgesia, reduce pain, alter the blood pressure, and depress respiration: substance P, which is the neurotransmitter in pain sensory neurons and may cause irritations and pain; and neuropeptide Y, which alters drinking and feeding behavior, alters blood pressure and body temperature, and influences memory functions. Because bio-regulators have the potential to be very active at extremely low doses, the detection of such agents is very important, but therefore, also very difficult to perform. Moreover, there are no commercially automatic detectors or alarms available

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that warn of the possible use of these new threat agents. However, the recent scientific developments in biotechnology will provide us with new possibilities in improved detection and identification of such new, potential warfare agents.

Synthetic Viruses

Recent work by Cello and co-workers also has shown that it is possible to synthesize viruses, such as poliovirus, from commercially available precursor chemicals.[11] Short stretches of carefully arranged bases are produced commercially, sold for biotechnological research, and can be assembled into a complete, active virus.[11] Poliovirus, consisting of a single strand of RNA, is one of the simplest viruses to synthesize because its genetic sequence is relatively short. However, it is likely that it eventually will be possible to synthesize more massive and complex viruses and other pathogens, such as smallpox or viruses that do not exist in the nature. The recently published work illustrates that it is possible to produce bioactive material by means of relatively simple chemistry.[11] Furthermore, a modified mousepox virus that kills its victims by wiping out part of their immune system, has been created accidentally by an Australian research team.[12] Since such technology is available all over the world, it is possible that terrorist groups might turn to the production of such agents as weapons of terrorism or that production of such weapons is carried out by independent states. At present, comprehensive, ongoing research in biology is underway to map the genome of different microbes, enabling us to have a better understanding of their physiological functions. The purpose is to understand how humans can better protect themselves against microbial infections. New technologies, such as genomics and proteomics, will play an important role in this work. Such mapping of microbial as well as the human genomes will provide us with detailed information on the functions and limitations, and will provide information about possibilities for production of new threat agents. Production of such agents would be in violation of existing disarmament treaties on biological and chemical weapons.

Genocidal Agents

Modern biotechnology, including developments in microbiology, molecular biology, and genetic engineering, is revolutionizing research in medicine and biology and providing us with detailed information about human development, physiology, medicine, and evolution. Initial sequencing and analysis of the human genome has been completed.[13] This is the first vertebrate genome to be so extensively sequenced, although some work still remains to be done to produce a complete map of the human genome. This vast amount of information about the human genome may result in misuse for political objectives and such information can be misused for clandestine production of chemical and biological weapons.[14] Development of such weapons of mass extermination of humans also could be potential future weapons for genocide, e.g., ethnic weapons. It is known that racial differences exist regarding sensitivities to certain infectious agents, and if these differences are sufficiently pronounced, there is the prospect that such weapons might become a reality.[15] It is clear that advances in technology, particularly biotechnology, will affect the development of new weapons as well as their countermeasures. Such new agents might connote a new threat for several reasons: (1) enhanced toxicity emanating from bioengineered toxin production; (2) medical treatment may be unavailable; (3) the agents might defeat presently available protective equipment; or (4) the production volume of new agents may be increased as well as the variety of agents might become larger. In addition to a possible threat from enhanced bacterial and viral virulence from the introduction of new genetic elements, the introduction of genetic material causing expressions of toxic substances not normally occurring in the strain also may become a reality. Research into such enhanced virulence was apparently conducted in the former Soviet Union approximately 20 years after the date of signature of the "Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction" in 1972.[16]

Drugs Produced in the Pharmaceutical Industry

Modern organic chemical synthesis and bio-techniques are revolutionizing the pharmaceutical industry and the production of new drugs for treatment of human and animal diseases. This rapid development in medical research and production of drugs also may be misused for clandestine production of chemical and biological weapons, including the production of new, effective, mid-spectrum warfare agents. Such production would be a violation of both the "Chemical Weapons Convention"[2] and "The Biological and Toxin Weapons Convention".[3]

For many years, bio-regulators and biotoxins have been of great interest due to their dramatic pharmacological effects. Some of these bio-regulators and biotoxins are being produced legally for medical and research purposes by the pharmaceutical industry and are in clinical use in the medical treatment of several diseases.[17-19] One example is botulinum toxins produced by the bacteria Clostridium botulinum, which produces several similar toxins that inhibit different proteins in the cholinergic nerve terminals, and thereby, block the release of the neurotransmittor acetylcholine. Efficacy of these biotoxins has been demonstrated in hemifacial spasms, dystonia, spasticity, hyperhidrosis, and other conditions.[17] Although use is prohibited by international law, some countries, including Iraq, have produced such toxins for to be used as weapons of mass destruction.[9,20]

Other mid-spectrum class drugs that are produced by the pharmaceutical industry and are in extensive clinical use, such as derivatives of the anaesthetic fentanyl, also have been used recently for riot control purposes to battle terrorist attacks in Moscow. Whether such use of mid-spectrum agents is in violation of the Chemical Weapons Convention is not clear as such use was "law enforcement purposes".[21]

Toxic Industrial Chemicals (TICs)

Finally, an increasingly important issue concerning the protection of military and peacekeeping forces from chemical

Bioregulators
Substance P
Neurokinin A
Opioids (endorphins and enkephalins)
Neuropeptide Y
Vasopressin
Cholecystokinin
Somatostatin
Neurotensin
Bombesin
Biotoxins
Botulinum toxin
Tetanus toxin
Saxitoxin
Diphteria toxin
Clostridium perferingens toxin
Ricin
T-2 Mycotoxin
Other animal-, bacterial-, fungal- and plant-toxins

Table 2—Examples of mid-spectrum agents

agents is the potential for exposure to chemical hazards such as TICs as well as to military-unique compounds during deployment for peacekeeping and peacemaking operations under the United Nations Charter. Military or civilian personnel who are deployed in support of such missions may be exposed to harmful chemicals as a result of industrial accidents, sabotage, or the intentional or unintentional actions of enemy or friendly forces. Another emerging threat is the alteration of the environment as a weapon of war such as by massive oil spills or setting oil wells on fire as was done by Iraq during the invasion of Kuwait in 1990. Exposure to toxic industrial chemicals, such as ammonia, chlorine, cyanides, corrosive substances, organo-solvents, heavy metals, fuels and fuel additives, pesticides, radioactive substances, and others or combination of such hazards were of great concern during deployment of military personnel in the former Republic of Yugoslavia in the 1990s. The authorities in those North Atlantic Treaty Organization (NATO) and Partnership for Peace countries who were supporting the operations in the Republic of Yugoslavia with military and civilian personnel considered these potential threats before the start of these peacekeeping operations. Improved intelligence collection and analysis is, therefore, of vital importance and is required to support preventive medicine and prevent unwanted exposures to toxic hazards from air and water pollution. Chemicals unique to the military include substances such as particular motor fuels, lubricating and cutting oils, cleaning solvents, rocket fuels, explosives, paints, de-icing substances, smokes, pesticides, etc. A higher level of safety and healthcare should be introduced to increase combat readiness and effectiveness and improve the probability of successful missions.

Role of International Prohibition

International Conventions

Following World War I, the 1925 Geneva Protocol prohibiting the use in war of both chemical and biological weapons was agreed. Many countries retained their rights to retaliate, in kind, in the event that such weapons should be used against them. After World War II, discussions to prohibit the development, production, and acquisition of chemical and biological weapons were held at the Conference on Disarmament in Geneva. These discussions in 1972 led to the opening for signature of the Biological and Toxin Weapons Convention, which prohibits development, production, acquisition, and stockpiling of these weapons.[3] The Convention entered into force in 1975. A new global treaty on chemical weapons including mid-spectrum agents was opened for signature in 1993. It prohibits the development, production, acquisition, and stockpiling of chemical weapons including toxins. The Chemical Weapons Convention, which entered into force in 1997, has provisions for verification of compliance.[2] This implies that the international community has a mandate to monitor destruction of all chemical weapons and carry out international inspections to completely preclude the possible use of chemical weapons. Such provisions do not exist in The Biological and Toxin Weapons Convention. As of May 2004, a total of 162 countries are state parties to the Chemical Weapons Convention.

There is little doubt that chemical weapons remain a threat even after the Chemical Weapons Convention went into effect in 1997. Several countries have not yet ratified the Convention and certain chemical weapons are relatively easy to produce from simple precursors (Table 1). However, such production, stockpiling, and use would be in violation of the Chemical Weapons Convention. As of 2004, there are two geographical areas of concern: (1) the Middle East where several countries have not yet signed or ratified the Convention (Egypt, Syria, Iraq, Lebanon, and Israel); and (2) the People's Republic of North Korea. None of these countries are states parties to the Chemical Weapons Convention and only some of these states are states parties to The Biological and Toxin Weapons Convention (as of November 2003, there are 151 states parties to the convention). Several of these countries also have comprehensive programs to develop and acquire means of delivery, such as long-range missile systems. From the inspections carried out in Iraq by the United Nations Special Commission, it was clear that Iraq was investing in a program to develop long-range missile systems with a range of up to 3,000 km.[8,10] This implies that almost all of the countries of Europe would be within range of such delivery systems.

Furthermore, several countries, which are states parties to the Chemical Weapons Convention, have declared possession of large stockpiles of various chemical weapons. As of August 2002, four countries have informed the Organization for the Prohibition of Chemical Weapons that they have chemical weapons amounting to nearly 70,000 metric tons of toxic agents. By May 2002, only about 10% of these stockpiles had been destroyed, mainly in the United States.[22-24] The Russian Federation is in the

Military threat from states which do not ratify the Chemical Weapons Convention or The Biological and Toxin Weapons Convention
Military threat against civilians and military forces participating in international operations
Military threat from new more effective classical chemical, biological and mid-spectrum warfare agents
Threat from chemical, biological and mid-spectrum warfare agents used by terrorists
Release of toxic industrial chemicals ("TICs") following bombing/ sabotage of production and storage sites

Table 3—The threat from chemical, biological and bottoxin agents

Nerveagents with new and more toxic properties
Weapons of genocide
Very poisonous biotoxins from plants and bacteria
Bio-regulators interacting with the human nervous-, immuno-, or hormonal systems
Agents where there are no automatic detectors or alarms available
Weapons causing long-term effects, such as cancer inducing agents
Mask breakers

Table 4—Possible new threat agents

early phases of commencing large-scale destruction of their chemical weapons stockpiles. These weapons were inherited from the former Soviet Union, and until these stockpiles are destroyed, the weapons continue to present a threat to all countries of the world if they are not kept under strict control.

In spite of these treaties, several countries, including Iraq, have used chemical warfare agents not only in conflicts with other countries, but also in domestic conflicts against their own population.

Final Considerations

It is crucial that the emergency medical services are well-prepared and recognize that casualties will result from the use of chemical warfare and mid-spectrum agents.[25] This requires a clear understanding of the likely threat from such weapons. Many threat-analysis scenarios have been performed and there is no clear answer to which chemical or mid-spectrum agents are the most likely immediate threats in chemical warfare or from chemical terrorism. It is well-understood, however, that there is no generic protection against all possible chemical or mid-spectrum warfare agents. Hence, it is important to create a civil and military defense system against the most likely warfare-agent threats. This should include proper information and analysis systems and effective protective equipment, stockpiles of antidotes such as vaccines and antisera against biotoxins where such antidotes exist, decontamination equipment, detection equipment, and analytical means to determine the presence of chemical, mid-spectrum, or biological warfare agents. In addition, it is essential to maintain military and civilian healthcare providers who have the knowledge and ability to specifically recognize symptoms of exposure to such warfare agents early, as well as the necessary medical and support drugs available for rapid use.

Conclusion

The future requires that all countries carefully evaluate and continuously assess the evolving threat from chemical weapons, mid-spectrum agents, and biological weapons. In view of the development of better protective equipment, electronic detectors, and medical countermeasures against existing warfare agents, the threat will change over time, and the use of certain already well-known agents will become less appealing (Table 4).

The final and key question is, can we or must we live with the threats posed by chemical, mid-spectrum, and biological warfare agents? First of all, we are able to live with the threat from such agents if nations improve their surveillance and intelligence gathering efforts and improve the physical and medical protection against likely warfare agents to an acceptable standard, including detection and decontamination capabilities in the civilian emergency sector. It is also of crucial importance to carry out regular exercise and training activities for military and civilian emergency personnel. In addition to national legislation and export control measures, it will be necessary to reduce the threat from weapons of mass destruction by implementing international verifiable agreements worldwide, such as the "Chemical Weapons Convention" and "The Biological and Toxin Weapons Convention", and to enable the United Nations to become a more effective body in maintaining international law and order.

Secondly, we must live with the threat from these weapons because of the instability of certain regions in the world and with the illegal production of chemical warfare agents, biotoxin agents, and micro-organisms that thereby is carried out. We must live with the fact that there are several so called "rogue states" that presumably produce threat agents in breach of international conventions prohibiting biological, chemical, and toxin weapons, as well as the reality that establishment of and operation of terrorist organizations is likely to encourage more nations or terrorist

groups to develop such weapons as weapons of mass destruction. Continuous and enhanced research efforts and training in all democratic countries can improve the existing medical and physical protective measures against chemical and biological weapons and mid-spectrum agents. The ultimate results of such combined efforts will decrease our vulnerability and improve our survivability, and thereby decrease the threat of use of such weapons.

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