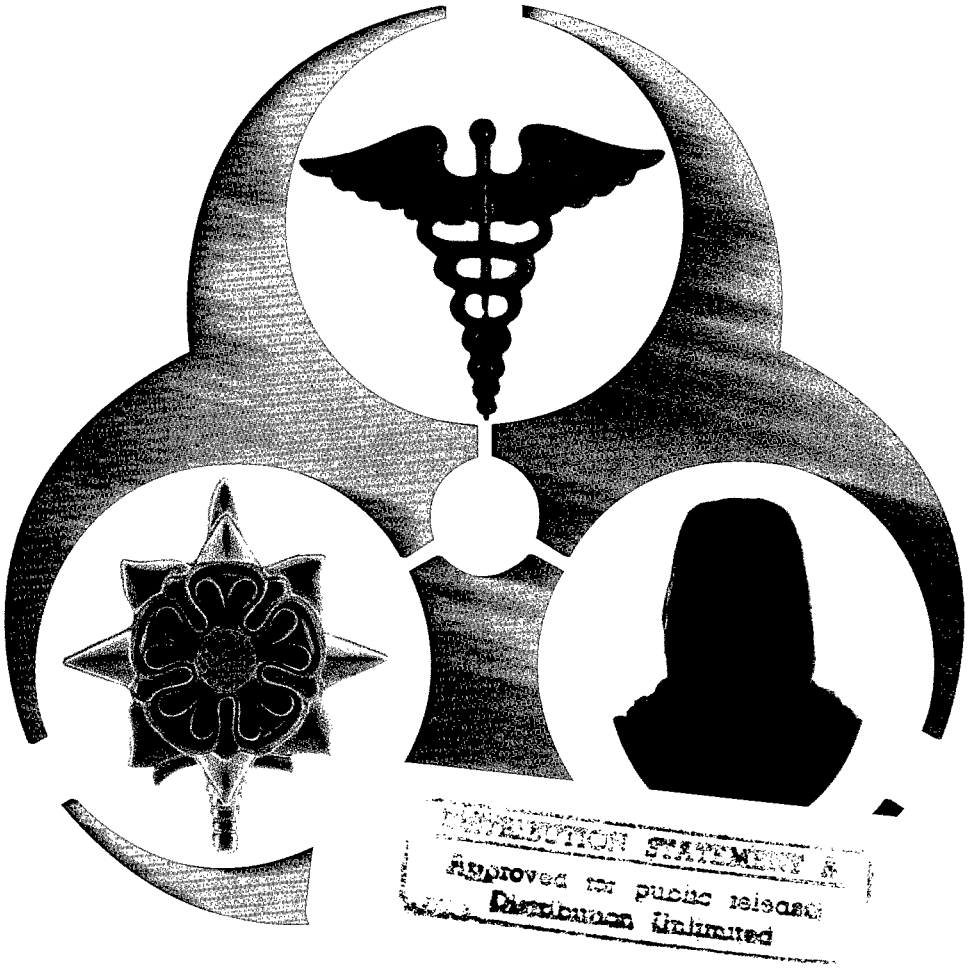
DEFENSE AGAINST TOXIN WEAPONS



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1998

PREFACE

The contents of this document are not to be construed as an official Department of the Army position unless so designated by other authorized documents. Opinions are those of the author and do not necessarily reflect doctrine.

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DEFENSE AGAINST TOXIN WEAPONS

INTRODUCTION

The purpose of this manual is to provide basic information on biological toxins to military leaders and health-care providers at all levels to help them make informed decisions on protecting their troops from toxins. Much of the information contained herein will also be of interest to individuals charged with countering domestic and international terrorism. We typically fear what we do not understand. Although understanding toxin poisoning is less useful in a toxin attack than knowledge of cold injury on an Arctic battlefield, information on any threat reduces its potential to harm. I hope that by providing information about the physical characteristics and biological activities of toxins, the threat of toxins will actually be reduced. I did not intend to provide detailed information on individual threat toxins or on medical prevention or treatment. This primer puts toxins in context, attempts to remove the elements of mystery and fear that surround them, and provides general information that will ultimately help leaders make rational decisions, protect their soldiers and win battles.

The mission of the U.S. Army Medical Research and Development Command's Medical Biological Defense Research Program is to study and develop means of medically defending the U.S. Armed Forces from toxins and infectious threats posed by adversaries. It is our responsibility to develop medical countermeasures to toxins of plant, animal and microbial origin. We believe that there is a biological toxin threat and we know of countries that are not in compliance with the Biological Weapons Convention of 1972. Therefore, prudence mandates a strong defensive program. The toxins described herein are all nonreplicating agents; some have been identified by the intelligence community as biological warfare threats.

Physical measures, such as the protective mask and decontamination systems, developed for the chemical threat are, for the most part, effective against toxin threats. Research to develop individual medical countermeasures to toxins is complicated by several factors. A number of toxins could be selected by an adversary for use in low-tech, relatively inexpensive weapons. Many more are potentially available through genetic engineering or chemical synthesis. Biological weapons are far more easily obtained and used than nuclear weapons. They actually may be more easily

produced and used than conventional explosive weapons. Colorless, tasteless, odorless, small-scale aerosols may be generated relatively easily with a cheap plastic nebulizer attached to a pump or pressurized air bottle. However, production and use of toxins as true mass casualty weapons is not a trivial undertaking.

The likely route of intoxication for soldiers or victims of terrorist attack is through the lung by respirable aerosols; another possibility is through the gastrointestinal tract by contamination of food or water supplies, although the latter would be difficult in chlorinated water, or in rivers, lakes or reservoirs because of dilution effects. The effects of most toxins are more severe when inhaled than when they are consumed in food or injected by bites or stings. Some toxins can elicit a significantly different clinical picture when the route of exposure is changed, a phenomenon that may confound diagnosis and delay treatment.

Finally, because the primary population at risk is relatively small (military troops, not the general public, as with childhood infectious diseases), there is little commercial incentive to produce vaccines, antisera or therapeutic drugs to counter toxin threats.

There are still many unknowns regarding toxins and their weaponization. Statements in this document on the nature of a "typical toxin attack" are based on my understanding of the physical characteristics of toxins, recent studies of aerosolized toxins in small laboratory chambers to test protective drugs and vaccines, and historical data from larger-scale studies with toxin or simulant aerosols.

The following three descriptions, **Toxin, Mass Casualty Biological (toxin) Weapon** and **Militarily Significant Weapon,** define these terms for the purposes of this primer.

1. A **Toxin** is any toxic substance that can be produced by an animal, plant or microbe. Some toxins can also be produced by molecular biologic techniques (protein toxins) or by chemical synthesis (low molecular weight toxins). Chemical agents, such as soman, sarin, VX, cyanide and mustard agents, typically man-made for weaponization, are not included in this discussion except for comparison.

2. A **Mass Casualty Biological (toxin) Weapon (MCBW)** is any toxin weapon capable of causing death or disease on a large scale, such that the military or

civilian infrastructure of the state or organization being attacked is overwhelmed. (Note: The commonly accepted term for this category of weapons is "Weapons of Mass Destruction," although that term brings to mind destroyed cities, bomb craters and great loss of life; MCBWs might cause loss of life only. I do not anticipate that "MCBW" will replace the term "Weapon of Mass Destruction" in common usage, but it is technically more descriptive of toxin weapons).

3. A **Militarily Significant (or Terrorist) Weapon** is any weapon capable of affecting—directly or indirectly, physically or through psychological impact—the outcome of a military operation.

UNDERSTANDING THE THREAT

The following is a theoretical discussion based on an understanding of physical and biochemical characteristics of toxins. It is not an intelligence assessment of the threat.

TOXINS COMPARED TO CHEMICAL WARFARE AGENTS

Toxins differ from classical chemical agents by source and physical characteristics. When considering how to protect soldiers from toxins, physical characteristics are much more important than source.

Table 1. compares both types of agents.

Table 1. Comparison of Chemical Agents and Toxins

TOXINS	CHEMICAL AGENTS
Natural origin	Man-made
Difficult, small-scale production	Large-scale industrial production
None volatile	**Many volatile**
Many are more toxic	Less toxic than many toxins
Not dermally active*	**Dermally active**
Legitimate medical use	No use other than as weapons
Odorless and tasteless	Noticeable odor or taste
Diverse toxic effects	Fewer types of effects
Many are effective immunogens**	Poor immunogens
Aerosol delivery	Mist/droplet/aerosol delivery

*Exceptions are trichothecene mycotoxins, lyngbyatoxin and some of the blue-green algal toxins. The latter two cause dermal injury to swimmers in contaminated waters, but are generally unavailable in large quantities and have low toxicity, respectively.
**The human body recognizes them as foreign material and makes protective antibodies against them.

The most important differences to understand are **volatility** and **dermal activity**. Toxins also differ from bacterial agents (e.g.: those causing anthrax or plague) and viral agents (such as those that cause VEE, smallpox, flu, etc.), in that toxins do not reproduce themselves.

TOXINS ON THE BATTLEFIELD

Because toxins are not volatile, as are chemical agents, and with rare exceptions, do not directly affect the skin, an **aggressor would have to present toxins to target populations in the form of respirable aerosols,** which allow contact with the more vulnerable inner surfaces of the lung. This, fortunately, complicates an aggressor's task by limiting the number of toxins available for an arsenal. Aerosol particles between 0.5 and 5 μm in diameter are typically retained within the lung. Smaller particles can be inhaled, but most are exhaled. Particles larger than 5-15 μm lodge in the nasal passages or trachea and do not reach the lung. A large percentage of aerosol particles larger than 15-20 μm simply drop harmlessly to the ground. Because they are not volatile, they are no longer a threat, even to unprotected troops. Although there are few data on aerosolized toxins, it is unlikely that secondary aerosol formation caused by vehicular or troop movement over ground previously exposed to a toxin aerosol would generate a significant threat; this may not be true with certain chemicals or with very heavy contamination with infectious agents such as anthrax spores.

TOXICITY, EASE OF PRODUCTION AND STABILITY

Because they must be delivered as respirable aerosols, toxins' utility as effective **MCBW** are limited by their toxicities and ease of production. The laws of physics dictate how much toxin of a given toxicity is needed to fill a given area of space with a small-particle aerosol. **Figure** 1 presents a theoretical calculation of the approximate quantities of toxins of varying toxicities required to intoxicate people exposed in large open areas on the battlefield under optimal meteorological conditions. The figure is based on a mathematical model that has been field tested and found to be valid. It shows that a toxin with an aerosol toxicity of 0.025 μg/kg would require 80 kg of toxin to cover 100 km^2 with an effective cloud exposing individuals to approximately a lethal dose 50 (LD_{50}). $\mathbf{LD_{50}}$ means, for example, that a person weighing 70 kg would have a 50% chance of surviving after receiving a 70 μg dose of a toxin with an LD_{50} of 1.0 μg/kg. Note that for toxins less toxic than botulinum or the staphylococcal enterotoxins, hundreds of kilograms or even ton quantities would be need to cover an area of 10x10 km (100 km^2) with an effective aerosol. Assuming this to be true, the number of toxins which can be used as **MCBW** is very limited; most of the

less toxic agents either cannot be produced in quantity with current technology, or delivered to cover large areas of the battlefield. That could change, however, especially for the peptide toxins, as techniques for generating genetic recombinants improve. Stability of toxins after aerosolization is also an important factor, because it further limits toxin weapon effectiveness.

It is readily apparent that, ignoring other characteristics, if a toxin is not adequately toxic, sufficient quantities cannot be produced to make even one weapon. Because of low toxicity, hundreds of toxins can be eliminated as ineffective for use in MCBWs. Certain plant toxins, with marginal toxicity, could be produced in large (ton) quantities. These toxins could possibly be weaponized. At the other extreme, several bacterial toxins are so lethal that MCBW quantities are measured not in tons, but in kilograms — quantities more easily produced. Such toxins are potential threats to our soldiers on the battlefield.

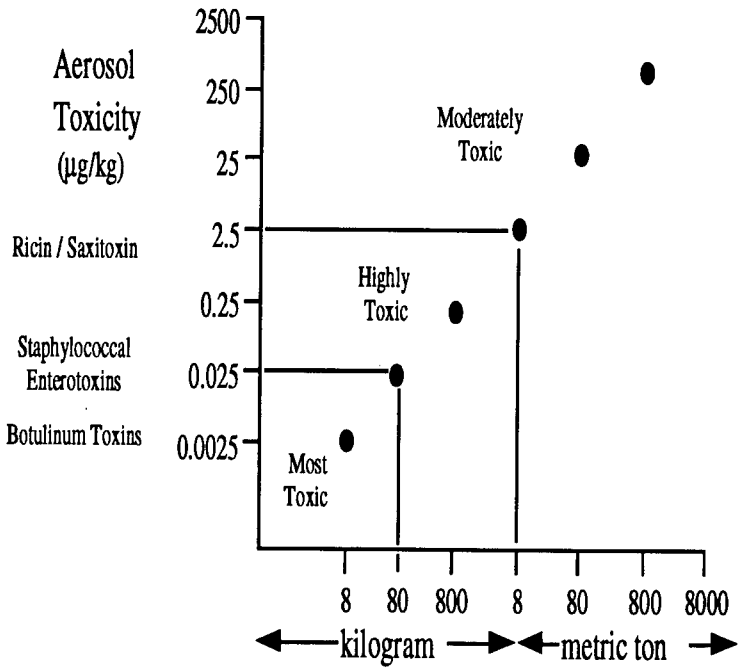

Figure 1. Toxicity in LD_{50} (see Table 2) vs. quantity of toxin required to provide a theoretically effective open-air exposure, under ideal meteorological conditions, to an area 100 km^2. (Patrick and Spertzel, 1992: based on Calder K.L., BWL Tech Study #3, Mathematical models for dosage and casualty coverage resulting from single point and line source release of aerosol near ground level, DTIC# AD310-361, Dec. 1957.) Ricin, saxitoxin and botulinum toxins kill at the concentrations depicted; the staphylococcal enterotoxins incapacitate.

Incapacitation, as well as lethality, to humans must be considered. A few toxins cause illness at levels many times less than the concentration needed to kill. For example, toxins that directly affect membranes and/or fluid balance within the lung may greatly reduce gas transport without causing death. Less potent toxins could also be significant threats as aerosols in a confined space, such as the air-handling system of a building. Finally, breakthroughs in delivery vehicle efficiency or toxin "packaging" by an aggressor might alter the relationship between toxicity and quantity, as depicted in **Figure** 1; but even at best, quantities needed could likely be reduced only by one-half for a given toxicity. For now, however, the figure provides a reasonable and valid way of sorting toxins.

Some toxins are adequately toxic and can be produced in sufficient quantities for weapons, but are too unstable in the atmosphere to be candidates for weaponization. Although stabilization of naturally unstable toxins and enhanced production of those toxins now difficult to produce are possibilities for the future, there exists no evidence at this time for successful amplification of toxicity of a naturally occurring toxin.

Militarily significant weapons need not be MCBW From 18 January to 28 February 1991, some 39 Iraqi-modified Scud missiles reached Israel. Although many were off target or malfunctioned, some of them landed in and around Tel Aviv. Approximately 1,000 people were treated as a result of missile attacks, but only two died. Anxiety was listed as the reason for admitting 544 patients and atropine overdose for hospitalization of 230 patients. (Karsenty *et al.*, Medical Aspects of the Iraqi Missile Attacks on Israel, Isr J Med Sci 1991: 27: 603-607). Clearly, these Scuds were **not effective mass casualty weapons, yet they caused significant disruption to the population of Tel Aviv.** Approximately 75% of the casualties resulted from inappropriate actions or reactions on the part of the victims. Had one of the warheads contained a toxin which killed or intoxicated a few people, the "terror effect" would have been even greater. Therefore, many toxins that are not sufficiently toxic for use in an open-air MCBW could probably be used to produce a militarily significant weapon. However, the likelihood of such a toxin weapon causing panic among military personnel decreases when the leaders and troops become better educated regarding toxins.

CLASSES AND EXAMPLES OF TOXINS

The most toxic biological materials known are **protein toxins produced by bacteria.** They are generally more difficult to produce on a large scale than are the plant toxins, but are many, many times more toxic. Botulinum toxins (seven related toxins), the staphylococcal enterotoxins (also seven different toxins), diphtheria and tetanus toxin are well-known examples of bacterial toxins. The **botulinum toxins** are so very toxic that lethal aerosol MCBW weapons could be produced with quantities of toxin that are attainable relatively easily with present technology. They cause death through paralysis of respiratory muscles. **Staphylococcal enterotoxins,** when inhaled, cause fever, headache, diarrhea, nausea, vomiting, muscle aches, shortness of breath, and a nonproductive cough within 2-12 hours after exposure; they can also kill, but only at much higher doses. Staphylococcal enterotoxin B (SEB) can incapacitate at levels at least one hundred times lower than the lethal level. These too would likely be delivered as a respirable aerosol.

Other bacterial toxins, classified generally as membrane-damaging, are derived from *Escherichia coli* (hemolysins), *Aeromonas, Pseudomonas* and *Staphylococcus alpha,* (cytolysins and phospholipases),

and are moderately easy to produce, but vary a great deal in stability. Many of these toxins affect body functions or even kill by forming pores in cell membranes. In general, their lower toxicities make them less likely battlefield threats.

A number of the **toxins produced by marine organisms or by bacteria that live in marine organisms** might be used to produce terrorist biological weapons. **Saxitoxin**, the best known example of this group, is a sodium-channel blocker and is more toxic by inhalation than by other routes of exposure. Unlike oral intoxication with saxitoxin (paralytic shellfish poisoning), which has a relatively slow onset, saxitoxin can be lethal in a few minutes by inhalation. Saxitoxin could be used against our troops as an antipersonnel weapon, but because it cannot currently be chemically synthesized efficiently, or produced easily in large quantities from natural sources, it is unlikely to be seen as an area aerosol weapon on the battlefield. **Tetrodotoxin** is much like saxitoxin in mechanism of action, toxicity and physical characteristics. **Palytoxin**, from a soft coral, is extremely toxic and quite stable in impure form, but difficulty of production or harvest from nature reduces the likelihood of an aggressor using it as an MCBW. The **brevetoxins**,

produced by dinoflagellates, and the blue-green algal toxins like the hepatotoxin, **microcystin**, have limited toxicity. For many of these toxins, either difficulty of production or lack of sufficient toxicity limits the likelihood of their use as MCBW.

The **trichothecene mycotoxins**, produced by various species of fungi, are also examples of low molecular weight toxins (molecular weight: 400-700 daltons). The yellow rain incidents in Southeast Asia in the early 1980s are believed to have demonstrated the utility of T-2 mycotoxin as a biological warfare agent. T-2 is one of the more stable toxins, retaining its bioactivity even when heated to high temperatures. High concentrations of sodium hydroxide and sodium hypochlorite are required to detoxify it. Aerosol toxicities are generally too low to make this class of toxins useful to an aggressor as an MCBW as defined in Figure 1; however, unlike most toxins, these are dermally active. Clinical presentation includes nausea, vomiting, weakness, low blood pressure, and burns in exposed areas.

Toxins derived from plants are generally very easy to produce in large quantities at minimal cost in a low-tech environment. A typical plant toxin is **ricin**, a protein derived from the bean of the

castor plant. Approximately 1 million tons of castor beans are processed annually worldwide in the production of castor oil. The resulting waste mash is 3-5% ricin by weight. Because of its marginal toxicity, at least a ton of the toxin would be necessary to produce an MCBW (as defined in **Figure 1**). Unfortunately, the precursor raw materials are available in those quantities throughout the world.

Animal venoms often contain a number of protein toxins as well as non-toxic proteins. Until recently, it would have been practically impossible to collect enough of these materials to develop them as biological weapons. However, many of the venom toxins have now been sequenced (their molecular structure is known) and some have been cloned and expressed (produced by molecular biological techniques). Some of the smaller ones could also be produced by relatively simple chemical synthesis methods. Examples of the venom toxins are 1) the **ion channel (cationic) toxins,** such as those found in the venoms of the rattlesnake, scorpion and cone snail; 2) the **presynaptic phospholipase A2 neurotoxins** of the banded krait, Mojave rattler and Australian taipan snake; 3) the **postsynaptic (curare-like alpha toxin) neurotoxins** of the coral, mamba, cobra, sea snake and cone snail; 4) the membrane-

damaging toxins of the Formosan cobra and rattlesnake and 5) the **coagulation/anti-coagulation toxins** of the Malayan pit viper and carpet viper. Some of the toxins in this group must be considered potential future threats to our soldiers as large-scale production of peptides becomes more efficient; however, difficulty of production in large quantity presently may limit the threat potential of many of them.

HOW TOXINS WORK

Unlike chemical agents, there are many classes of toxins, and they differ widely in their mechanisms of action. This makes the job of medically protecting soldiers difficult, as there are seldom instances where one vaccine or therapy would be effective against more than one toxin. Time from exposure to onset of clinical signs may also vary greatly among toxins.

(Note that, unlike a terrorist threat, one can prepare for a battlefield threat through development of specific medical countermeasures. Vaccines and other prophylactic measures can be given before combat, and therapies kept at the ready.)

Some neurotoxins, such as **saxitoxin**, can kill an individual very quickly (minutes) after inhalation of a lethal dose. This toxin acts by **blocking nerve conduction directly** and causes death by paralyzing muscles of respiration. Yet, at just less than

a lethal dose, the exposed individual may not even feel ill or just dizzy. Because of the rapid onset of signs after inhalation, prophylaxis (immunization or pretreatment with drugs) would be required to protect soldiers from these rapidly acting neurotoxins. Unprotected soldiers inhaling a lethal dose would likely die before they could be helped, unless they could be intubated (a breathing tube placed in the airway) and artificially ventilated immediately. Although the mechanism of death after inhalation of saxitoxin is believed to be the same as when the toxin is administered intravenously, it is more toxic (a smaller dose will kill) if inhaled.

Other neurotoxins, such as the **botulinum toxins, must enter nerve terminals before they can block the release of neurotransmitters** which normally cause muscle contraction. Botulinum neurotoxins generally kill by relatively slow onset (hours to days) respiratory failure. The intoxicated individual may not show signs of disease for 24-72 hours. The toxin blocks biochemical action in the nerves that activate the muscles necessary for respiration, leading to suffocation. Intoxications such as this can be treated with antitoxin (a preparation of antibodies from humans or animals) that can be injected hours (up to

24 hours in monkeys, and probably humans) after exposure to a lethal dose of toxin, and still prevent illness and death. Although the mechanisms of toxicity of the botulinum toxins appear to be the same after any route of exposure, unlike saxitoxin, the actual toxicity is less by inhalation (i.e., the lethal dose of botulinum toxin is slightly greater by inhalation).

While neurotoxins effectively stop nerve and muscle function without causing microscopic damage to the tissues, other toxins **destroy or damage tissue directly**. For these, prophylaxis (pretreatment of some kind) is important because the point at which the pathological change becomes irreversible often occurs within minutes or a few hours after exposure. An example of this type of toxin is **microcystin, produced by blue-green algae,** which binds very specifically to an important enzyme inside liver cells; this toxin does not damage other cells of the body. Unless uptake of the toxin by the liver is blocked, irreversible damage to the organ occurs within 15-60 minutes after exposure to a lethal dose. In this case, the tissue damage to a critical organ, the liver, is so severe that therapy may have little or no value. For this toxin, unlike most, the toxicity is the same, no matter what the route of exposure.

The consequences of intoxication may **vary widely with route of exposure**, even with the same toxin. The **plant toxin, ricin,** kills by blocking protein synthesis in many cells of the body, but no lung damage occurs with any exposure route except inhalation. If ricin is inhaled, as would be expected during a biological attack, microscopic damage is limited primarily to the lung, and that damage may be caused by a mechanism different from that which occurs if the toxin is injected. Furthermore, when equivalent doses of toxin are used, much more protective antibody must be injected to protect from inhalation exposure compared to intravenous injection of the toxin. Finally, although signs of intoxication may not be noted for 12-24 hours, microscopic damage to lung tissue begins within 8-12 hours or less. Irreversible biochemical changes may occur in 60-90 minutes after exposure, again making therapy difficult.

The toxicities of some bacterial toxins are too low to make them effective *lethal* MCBWs, according to the standards described in Figure 1. However, some cause incapacitating illness at extremely low levels. Therefore, lethality alone is not an appropriate criterion on which to base a toxin's potential as a threat. The **staphylococcal enterotoxins** are examples. They

can cause illness at extremely low doses, but relatively high doses are required to kill. These toxins are unusual, in that they act by causing the body to release abnormally high levels of certain of its own chemicals, which, in very small amounts, are beneficial and necessary for life, but at higher levels are harmful.

Only one class of easily produced toxins, the **trichothecene mycotoxins**, is **dermally active**. Therefore, trichothecenes must be considered by different standards than all other toxins. They can cause skin lesions and systemic illness without being inhaled and absorbed through the respiratory system. Skin exposure or ingestion of contaminated food are the two likely routes of exposure of soldiers; oral intoxication is unlikely in modern, well-trained armies. Nanogram (one billionth of a gram) quantities per square centimeter of skin cause irritation, and microgram (one millionth of a gram) quantities cause necrosis (destruction of skin cells). If the eye is exposed, microgram doses can cause irreversible injury to the cornea (clear outer surface of the eye). The aerosol toxicity of even the most toxic member of this group is low enough that large-quantity production (approximately 80 metric tons to expose a 10 km^2 area with respirable aerosol) makes

an inhalation threat unlikely on the battlefield. These toxins, therefore, might be dispersed as larger particles, probably visible in the air and on the ground and foliage. In contrast to treatment for exposure to any of the other toxins, simply washing the skin with soap and water within 1-3 hours after an exposure would eliminate or greatly reduce the risk of illness or injury.

MANY TOXINS, BUT NOT AN OVERWHELMING PROBLEM

Because there are hundreds of toxins available in nature, the job of protecting troops against them seems overwhelming. One would think that an aggressor would need only to discover the toxins against which we can protect our troops and pick a different one to weaponize. In reality, it is not quite that simple. The utility of toxins as MCBWs is limited by toxicity (**Figure 1**). This criterion alone reduces the list of potential open-air, weaponizable toxins for MCBWs from hundreds to fewer than 20. Issues related to stability and weaponization will not be addressed here, but would only further reduce the list and make the aggressor's job more difficult.

POPULATIONS AT RISK

An armored or infantry division in the field is not at great risk of exposure to a marine toxin whose toxicity is such that 80 tons are needed to produce an MCBW covering 10 km^2. Most marine toxins are simply too difficult to produce in such quantities. Military leaders on today's battlefield should be concerned first about the most toxic bacterial toxins and possibly some of the plant toxins that are slightly less toxic but available in large quantities in nature.

The more confined the military or terrorist target (e.g., inside shelters, buildings, ships or vehicles) the greater the list of potential toxin threats which might be effective. This concern is countered, however, by the fact that toxins are not volatile like the chemical agents and are thus more easily removed from air-handling systems than are volatile agents. It is probably most cost-effective to protect our personnel from these toxins through the use of collective filtration systems.

Nonetheless, we must consider subpopulations of troops and areas within which they operate when we estimate vulnerability to a given toxin threat. Situations could well occur in which different populations of troops require protection from different toxins, because of differences in

operational environments. To protect them effectively, decision makers and leaders must understand the nature of the threat and the physical and medical defense solutions.

Table 3 lists the approximate number of known toxins by toxicity level and source. To simplify our approach to development of medical countermeasures, we have divided them into "Most Toxic," "Highly Toxic" and "Moderately Toxic" categories (also see Figure 1). The Most Toxic toxins could probably be used in an MCBW; it is feasible to develop **individual medical countermeasures** against them. The Highly Toxic toxins could probably be used in closed spaces such as the air-handling system of a building or as ineffective terror weapons in the open; **collective filtration** would be effective against these toxin aerosols targeted to enclosed spaces. The Moderately Toxic toxins would likely be useful only as assassination weapons which would require direct attack against an individual; it is not feasible to develop medical countermeasures against all of the toxins in this group. Such reasoning allows us to use limited resources most effectively and maximize protection, and thus effectiveness, of our fighting force.

Source	Most Toxic	Highly Toxic	Moderately Toxic	Total
	(Number of toxins in each category)			
Bacterium	17	12	>20	>49
Plant		5	>31	>36
Fungus			>26	>26
Marine organism		>46	>65	>111
Snake		8	>116	>124
Alga		2	>20	>22
Insect			>22	>22
Amphibian			>5	>5
Total	17	>73	>305	>395

Table 3. Approximate number of toxins arbitrarily categorized as Most Toxic (LD_{50} <0.025 μg/kg), Highly Toxic (LD_{50}, 0.025-2.5 μg/kg) and Moderately Toxic (LD_{50} >2.5 μg/kg). From DNA-TR-92-116, Technical Ramifications of Inclusion of Toxins in the Chemical Weapons Convention (CWC).

COUNTERMEASURES

PHYSICAL PROTECTION

As stated above, most toxins are neither volatile nor dermally active. Therefore, an aggressor would most likely attempt to present them as respirable aerosols. Toxin aerosols should pose neither significant residual environmental threat, nor remain on the skin or clothing. The typical toxin cloud would, depending on meteorologic conditions, either drift with the wind close to the ground or rise above the surface of the earth and be diluted in the atmosphere. There may, however, be

residual contamination near the munition release point. Humans in the target area of a true aerosol would be exposed as the agent drifted through that area. The principal way humans are exposed to such a cloud is through breathing. Aerosol particles must be drawn into the lungs and retained to cause harm.

The protective mask, worn properly, is effective against toxin aerosols. Its efficacy is, however, dependent on two factors: 1) mask-to-face fit and 2) use during an attack. Proper fit is vital. Because of the extreme toxicity of some of the bacterial toxins, a relatively small leak could easily result in a significant exposure. Eyes should be protected when possible. Definitive studies have not been done to assess the effects of aerosolized toxins on the eyes. One would expect that, in general, ocular exposure to a toxin aerosol, unless the exposed individual is near the release point, would result in few systemic effects because of the low doses absorbed. Certain toxins have direct effects on the eyes, but these are generally not toxins we would expect to face as aerosols. Donning the protective mask prior to exposure would, of course, protect the eyes.

Because important threat biological warfare agents are not dermally active,

special protective clothing, other than the mask, is less important in at toxin attack than a chemical attack. Presently available clothing should be effective against biological threats as we know them. Commanders should carefully consider the relative impact of thermal load and the minimal additional protection provided by protective clothing.

REAL-TIME DETECTION OF AN ATTACK

Because of the nature of the threat, soldiers may be dependent on a mechanical detection and warning system to notify them of impending or ongoing attack. Without timely warning, their most effective generic countermeasure, the protective mask, may be of limited value. There have been successful efforts in the past to develop real-time detectors of a chemical agent attack. It will be more difficult to develop such detectors for toxins for several reasons. As stated above, toxins must be presented as respirable aerosols, which act as a cloud, not as droplets (as the chemical agents) that fall to the ground and evaporate with time. The toxin cloud, typically delivered at night with a slight wind, would be expected to move across the battlefield until it either rises into the atmosphere to be diluted or settles, relatively harmlessly, to the ground. Unlike chemical agents, which might be detectable for hours, toxins

might be detectable in the air at one location only for a few minutes. Definitive, specific toxin detectors would have to sample continuously or be turned on by a continuous sampler of some kind.

Furthermore, toxin detectors (assuming the present state of technology) would likely have to have the specificity of immunoassays to identify a toxin and differentiate it from other organic material in the air. Continuous monitoring by such equipment would be extremely costly, reagent intensive, and logistically very difficult to support because of reagent requirements. Identifying each toxin would require a different set of reagents if an immunoassay system were used. Analytical assays would necessarily be more complex and less likely to identify distinct toxins, but might detect that something unusual was present. Imagine the difficulty of developing a detection system based on molecular weight or other physical characteristics to differentiate among the seven botulinum toxins (molecular weight is the same for all of the botulinum toxins, while all seven require a different antibody for identification or therapy). Finally, to be effective, a detector would have to be located where it could "sniff" a toxin cloud in time to warn the appropriate population. This might be possible on a battlefield, but would be nearly impossible,

except in selected facilities, in the case of a terrorist attack. It is possible that, if all the capabilities described were developed and available at the right place and time, an aerosol cloud of almost any of the toxins of concern could be detected and identified. Future advances in technology could well resolve our present technical difficulties.

DIAGNOSIS: General Considerations

Health-care providers often ask whether they will be able to tell the difference among cases of inhalation botulinum, staphylococcal enterotoxin intoxication, and chemical nerve agent poisoning **Table 4.** describes these differences. In general, nerve agent poisoning has a rapid onset (minutes) and induces increased body secretions (saliva, airways secretions), pinpoint pupils and convulsions or muscle spasms. Botulinum intoxication has a slow onset (24-72 hours) and manifests as visual disturbance and muscle weakness, (often seen first as droopy eyelids). SEB poisoning has an intermediate (few hours) time of onset and is typically not lethal, but severely incapacitating. Chemical nerve agent poisoning is a violent illness resulting in respiratory failure because of muscle spasm, airway constriction and excessive fluid in the airways. Botulinum-intoxicated patients simply get very tired, very weak and, if they die, it is because the muscles of

respiration fail. SEB-intoxicated patients become very sick, but typically survive.

Health-care providers should consider toxins in the differential diagnosis, especially when multiple patients present with a similar clinical syndrome. Patients should be viewed epidemiologically and asked about where they were, whom they were with, what they observed, how many other soldiers were and are involved, etc. Inhaled and retained doses of toxins will differ among soldiers exposed to the same aerosol cloud. Those who received the highest dose typically will show signs and symptoms first. Others will present somewhat later, while others in the same group may show no signs of intoxication. The distribution of severities within the group of soldiers may vary with type of exposure and type of toxin. For example, exposing a group of individuals to the staphylococcal enterotoxins would likely make a large percentage (80%) of them sick, but would result in few deaths. Exposing a group of soldiers to a cloud of botulinum toxin might kill half, make 20% very sick, and leave 30% unaffected.

One must consider the varying latent periods before onset of clinical signs. For patients exposed to toxins by aerosol, the

latent or asymptomatic period varies from minutes (saxitoxin, microcystin) to hours (the staphylococcal enterotoxins), even to days (ricin, the botulinum toxins).

Save clinical and environmental samples for diagnosis. Both immunoassays and analytical tests are available for many of the toxins. Toxin samples taken directly from a weapon are often easier to test than biological samples because they do not contain body proteins and other interfering materials. The best early diagnostic sample for most toxins is a swab of the nasal mucosa. In general, the more toxic toxins are more difficult to detect in tissues and body fluids, because so little toxin needs to be present in the body to exert its effect. The capability exists however, to identify most of the important toxins in biological fluids or tissues, and many other toxins in environmental samples. Definitive laboratory diagnosis might take 48-72 hours; however, prototype field assays that can identify some toxins within 30 minutes have been developed recently. For individuals who survive an attack with toxins of lower toxicity, immunoassays that detect IgM or IgG (immunoglobulins produced by the body after exposure to a toxin) offer a means of diagnosis or confirmation or indirect identification of agent within 2-3 weeks after exposure.

APPROACHES TO PREVENTION AND TREATMENT

In developing medical countermeasures, each toxin must be considered individually. Some incapacitate so quickly that there would be little time for therapy after an attack. Others cause few or no clinical signs for many hours, but set off irreversible biochemical processes in minutes or a few hours which lead to severe debilitation or death several days later. Fortunately, some of the most potent bacterial protein toxins act slowly enough that, if they are identified, therapy is usually successful 12-24 hours after exposure.

It is always better to prevent casualties than to treat injured soldiers. For most of the significant threat toxins in military situations, **vaccination is the most effective means of preventing casualties.** Unlike the chemical warfare agents, many of the important threat toxins are highly immunogenic (exposing the body to small doses of the inactivated toxin causes the body to make antibodies that protect against subsequent actual toxin exposure). Immunized laboratory animals are totally protected from high-dose aerosols of these toxins. Immunization requires a knowledge of the threat, availability of a vaccine, and time. The time needed to allow the body to make its own protective antibodies to a

toxin may range from a minimum of 4-6 weeks to 12-15 weeks or longer. Some vaccines currently in use require multiple injections, often weeks apart. The logistical burden of assuring that troops are given booster immunizations at the correct time could be overwhelming in a fast-moving build-up to hostilities.

It may be possible to reduce the time required for immunization. For example, antigens (materials that stimulate the body to develop antibodies) are being microencapsulated (entrapped in a synthetic polymer that breaks down, slowly releasing the material) to form timed-release vaccines that might provide the primary immunization, a boost two weeks later, and another boost 10 weeks after that—all with one injection. Another approach is being evaluated with current Medical Biological Defense Research Program vaccines. Soldiers could be given a priming dose and the first boost two weeks apart while in basic training. The response generated by the immune system's memory cells might last for many months or even years, although not all soldiers would develop fully protective immunity at that time after two immunizations. Shortly before the onset of hostilities, or when the soldier is assigned to a rapidly deployable unit, one boost could provide protective immunity

quickly, and preclude the need for additional boosts after deployment. Preliminary data suggest that a boost up to 24 months (the greatest interval thus far tested) after two initial priming doses will be effective, even with moderately immunogenic vaccines such as the current botulinum toxoid. Studies are ongoing to determine the maximum reasonable interval between initial immunization series and the predeployment boost.

Passive antibody prophylaxis (the soldier doesn't make his own antibodies, but is given antibody preparations produced in animals or other humans)is generally quite effective in protecting laboratory animals from toxin exposure. However, this option is of little real utility for large groups of people for several reasons. The protection provided by human antibody may last for only 1-2 months, and protection afforded by despeciated (animal antibodies altered chemically to reduce the likelihood of the human body identifying them as foreign protein) horse antibody may last for only a few weeks. Therefore, antibody prophylaxis would be practical only when the threat is clearly understood and imminent. Furthermore, it is unlikely that animal antibody would be used in an individual before intoxication because of the risk, albeit

small, of an adverse reaction to foreign protein. The latter problem may be overcome within the next few years, as the production of human monoclonal antibodies (homogeneous populations of antibodies directed against one, very specific site on the toxin) or "humanization" of mouse monoclonal antibodies become practical. Unfortunately, single monoclonal antibodies are seldom as effective against toxins as polyclonal antibodies, such as those produced naturally in other humans or horses. However, combined antibody therapy, or "cocktails" of more than one monoclonal antibody, may overcome this problem in the future.

Pretreating soldiers with drugs is feasible, but little success has been achieved in the discovery or development of drugs that block the effects of toxins. Many toxins affect very basic mechanisms within body cells, tissues and organs; therefore, drugs that block these effects often have debilitating or toxic side effects. An exception is rifampin, the anti-tuberculosis drug, which protects laboratory animals exposed to the blue-green algal toxin, microcystin, and is safe for use in humans.

Pretreatment (treatment after exposure) with antibodies from human or animal sources is feasible for some of the

threat toxins. Passive immunotherapy (treatment with other than one's own antibodies) is very effective after exposure to botulinum toxin if treatment is begun soon enough, up to 24 hours after high-dose aerosol exposure to the toxin. The utility of antibody therapy drops sharply at or shortly after the onset of the first signs of disease. It appears that a significant amount of the toxin has, at that time, been taken up by areas of the body that cannot be reached by circulating antibodies. Even so, we have preliminary evidence that antibody therapy is at least partially effective after onset of signs of intoxication (36-48 hours after aerosol exposure) in monkeys exposed to botulinum toxin. The available antibody to botulinum toxin is produced in horses, and then despeciated to make a product with a reduced risk of adverse reaction that can be given to humans. Human monoclonal antibodies, or cocktails of two or more monoclonal antibodies, may be the next generation of antibody therapy. Passive antibody therapy such as that described here is more likely to be effective against neurotoxins like the botulinum toxins, which do not cause tissue damage, than against toxins that induce mediator release (the staphylococcal enterotoxins) or directly damage tissues (ricin).

Specific therapy with drugs (drugs that alter the action of the toxin or reverse its toxic effects directly) presently has little value because most of the toxins either physically damage cells and tissues very quickly (ricin), or affect such basic mechanisms within the cell (the neurotoxins) that drugs designed to reverse their effects are toxic themselves. Nevertheless, we have shown that rifampin stops the lethal intoxication by microcystin if given to laboratory animals therapeutically soon after toxin administration (within 15-30 min). **Development of therapeutic drugs for toxins is presently aimed at several more general approaches.** Where the mechanism of action of the toxin is understood and covalent (permanent) bonding of the toxin to cellular protein does not occur (example: ion-channel toxins), attempts are being made to discover drugs that compete or block the toxin from binding to its site of action. For toxins with enzymatic activities, such as ricin and the botulinum toxins, drugs that serve as alternate targets of such enzymatic action may be developed. For toxins such as botulinum, which block the release of a neural transmitter, attempts can be made to enhance the release of the needed transmitter by other means; the diaminopyridines are temporarily effective in reversing botulinum intoxication by this mechanism.

Finally, for toxins like staphylococcal enterotoxins and ricin, which induce the release of secondary mediators (actually, a natural part of the body's defense mechanism that overreacts), specific mediator blockers are being studied. It is likely that, in the next few years, drugs may find a place in the therapy of some intoxications as adjuncts to vaccination or passive antibody therapy, or they may be used to delay onset of toxic effects.

Other general supportive measures (Symptomatic Therapy) are likely to be effective in therapy of intoxication. Artificial ventilation could be life-saving in the case of neurotoxins, which block nerves that drive muscles of respiration (botulinum toxins and saxitoxin). Oxygen therapy, with or without artificial ventilation, may be beneficial for intoxication with toxins that directly damage the alveolar-capillary membrane (the site of movement of molecules between the inhaled air and the blood) of the lung. Vasoactive drugs (drugs that cause blood vessels to dilate or contract) and volume expanders could be used to treat the shock-like state that accompanies some intoxications. These measures could be used in conjunction with more specific therapies.

DECONTAMINATION: Is It Necessary?

Recall that a true respirable aerosol will leave less residue on clothing and environmental objects than would the larger particles produced by a chemical munition. This suggests that decontamination would be relatively unimportant after a toxin aerosol attack. Because we lack field experience, however, prudence dictates that soldiers decontaminate themselves after an attack. As a general rule, the decontamination procedure recommended for chemical warfare agents (Army FM 8-285) effectively destroys toxins. Exposure to 0.1% sodium hypochlorite solution (household bleach) for 10 minutes destroys most protein toxins. The trichothecene mycotoxins require more stringent measures to inactivate them, but even they can be removed from the skin (although not inactivated) simply by washing with soap and water. Soap and water, or even just water, can be very effective in removing most toxins from skin, clothing and equipment.

Again, because most toxins are not volatile or dermally active, decontamination is less critical than after a chemical attack.

ANSWERS TO OFTEN-ASKED QUESTIONS

PROTECTING HEALTH-CARE PROVIDERS

For the same reason that decontamination is only moderately important after personnel are exposed to a respirable toxin aerosol, health-care providers are probably at only limited risk from secondary aerosols. Because toxins are not volatile, casualties can, for the most part, be handled safely and moved into closed spaces or buildings, unless they were very heavily exposed. Prudence dictates, however, that patients be handled as chemical casualties or, at a minimum, that they be washed with soap and water. The risk to health-care providers is of greater concern with some agents. Secondary exposure might be a hazard with very potent bacterial protein toxins, such as botulinum toxin or the staphylococcal enterotoxins. (Note that decontamination and isolation of patients or remains could be much more important and difficult after an attack with a bacteria or virus that replicates within the body.)

Remains of persons possibly contaminated with toxins should be handled as chemically contaminated remains. For the most part, toxins are more easily destroyed than chemical agents, and they are much

more easily destroyed than spores of anthrax. Chemical disinfection of remains in 0.2% sodium hypochlorite solution for 10 minutes would destroy all surface toxin (and even anthrax spores), greatly reducing the risk of secondary exposure.

SAMPLE COLLECTION: General Rules for Toxins

Identifying toxins or their metabolites (break-down products) in biological samples (blood, urine, feces, saliva or body tissues) is difficult for several reasons. In the case of the most toxic toxins, relatively few molecules of toxin need be present in the body to cause an effect, therefore, "finding" them requires extremely sensitive assays. Secondly, the most toxic, and most likely to be seen on the battlefield, are proteins, a class of molecules which our bodies break down and process. Therefore, these toxins and pieces of them after breakdown often "blend into the scenery" of the body and, at some point, are no longer identifiable.

Typically, we must look for the toxin itself or its metabolites, not an antibody response, as can be done with infectious agents. It is very unlikely that anyone receiving a lethal dose of any of the toxins would live long enough to be able to mount an antibody response. However, with

certain protein toxins (ricin and the staphylococcal enterotoxins) that are highly immunogenic and less lethal, one might expect to see antibodies produced in soldiers who received a single exposure and survived. These might be seen as early as two weeks after exposure.

Certain toxins can be identified in the serum of animals, therefore probably humans, exposed by inhalation. Blood samples should be collected in sterile tubes and kept frozen, or at least cold, preferably after clotting and removal of cells. If collected within the first day, swab samples taken from the nasal mucosa may be useful in identifying several of the toxins. These too, should be kept cold. As a general rule, all samples that are allowed to remain at room temperature (approximately 75-80^{0}F) or above for any length of time will have little value.

Biological samples from patients are generally not as useful for diagnosis of intoxications as they are for diagnosis of infectious diseases. The same is true of postmortem samples. The literature suggests that botulinum toxins can be isolated from liver and spleen, even when they cannot be isolated from blood. We can identify ricin with immunoassays in extracts of lung, liver, stomach and intestines up to 24 hours

after aerosol exposure. We have identified high doses of ricin in fixed lung tissue of aerosol-exposed laboratory animals by immunohistochemical methods. The staphylococcal enterotoxins can be detected by immunoassay in bronchial washes. Like blood and swab samples, postmortem tissue or fluid samples should be kept cold, preferably frozen, until they can be assayed.

Environmental samples from munitions or swabs from environmental materials should be placed in sealed glass or Teflon® containers, and kept dry and as cold as possible. Handling a dry or powdered toxin can be very dangerous, because the toxin may adhere to skin and clothing and could be inhaled.

TOXIN ANALYSIS AND IDENTIFICATION

Immunological and/or analytical assays are available for most of the toxins discussed in this document. Immunological methods, typically enzyme-linked immunosorbent assays (ELISA) or receptor-binding assays, are sensitive to 1-10 nanograms/milliliter and require approximately 4 hours to complete; these are being developed as the definitive diagnostic tests for deployment. Analytical (chemical) methods are sensitive at low microgram to high nanogram amounts, and take approximately 2 hours to run, plus time for instrument

setup and isolation or matrix removal when necessary; the latter can add days to the process. A small, sensitive, far-forward, fieldable assay for several toxins has been developed and similar kit assays are being developed for many of the other toxins described in this document. The polymerase chain reaction (PCR) technique, which provides very sensitive means of detecting and identifying the genetic material (DNA) of any living organism, can be used to detect remnants of the bacterial, plant or animal cells that might remain in the crude, impure toxin one would expect to find in a weapon. Finally, a new method of combining immunoassays with PCR may allow us to detect extremely small quantities of the toxins themselves. In their present state, PCR assays are primarily suited for use in the reference laboratory.

WATER TREATMENT

Questions often arise regarding the protection of water supplies from toxins. It is unlikely that a typical small-particle aerosol attack with toxins would significantly contaminate water supplies. Furthermore, as a general rule, direct contamination of water supplies by pouring toxins into the water would require that it be done downstream of the processing plant and near the end user, even for the most toxic bacterial toxins—and normal chlorination methods

are effective against some of the most potent toxins. Because of dilution, adding toxins to a lake or reservoir would be unlikely to cause human illness. Natural production of algal toxins (e.g., microcystin) in stagnant bodies of water could produce enough toxin to cause illness if that water were used for drinking. The following methods of water purification have been tested for the toxins listed.

Reverse osmosis systems are effective against:

Ricin—64,000 daltons (molecular weight)

Microcystin—1,000 daltons

T-2—466 daltons

Saxitoxin—294 daltons

(Botulinum toxin—150,000 daltons and SEB—28,494 daltons not tested: expect same result)

Coagulation/flocculation

Not effective for removing ricin, microcystin, T-2 or saxitoxin from water.

Chlorine

Five milligrams/liter (5 parts per million) free, available chlorine (household bleach) for 30 minutes destroys botulinum toxin. This concentration does not inactivate ricin, microcystin, T-2 or saxitoxin.

THE FUTURE

INTELLIGENCE: Information that protects soldiers

Readers of this document should now understand several important points about protecting soldiers and targets of terrorist attack from toxin weapons:

1) Fifteen to twenty of some 400 known toxins have the physical characteristics that make them threats against U.S. forces as potential **MCBWs**. However, many toxins could be used in weapons to produce **militarily significant/terrorist (psychological) effects**—especially in poorly educated troops or in uninformed civilian populations.

2) Effective individual physical protective gear is available; soldiers must receive timely warning of an attack, however, if they are to use their protective masks effectively.

3) Most of the toxins with the characteristics that make them threats as MCBW are proteins, which is to our advantage; vaccines or passive antibody therapy are developed relatively easily.

4) Immunizing troops, much preferred to treating intoxicated troops after exposure, typically requires a minimum of 4-15 weeks.

5) Development of medical countermeasures against likely MCBWs is feasible.

In addition, research for and development of a vaccine or passive antibody therapy through final approval by the U.S. Food and Drug Administration as a product for human use is likely to require a minimum of 4-7 years (8-10 years in some cases). Because developing and producing countermeasures takes years, intelligence information regarding toxin research for weapons development and aggressor capability analysis is invaluable. Our own understanding of the physical characteristics of toxins, even without intelligence information, allows us to deduce what may be possible for the aggressor; this information reduces the list of toxins from hundreds to less than 20. Good intelligence on threat research and development can, at a minimum, help those responsible for research and development of medical countermeasures prioritize finite resources, and thus reduce the time of the research and development cycle. Good intelligence on weaponized toxins held by an aggressor will also greatly assist leaders who must make decisions to immunize troops as they prepare for conflict. Therefore, as regards medical defense against toxin weapons, a strong and effective intelligence effort is both necessary and cost-effective.

TOXINS AS WEAPONS

Research literature suggests that we have discovered the majority of the "most toxic" (LD_{50} < 0.0025 micrograms/kilogram) naturally occurring toxins. New toxins of lesser toxicity, especially the venom toxins, are being discovered at the rate of perhaps 10-30 per year. There is little precedence in the literature for artificially increasing the toxicities of naturally occurring toxins; however, it might be possible to increase the physical stability of toxins that are toxic enough but too unstable to weaponize. This could increase the effectiveness of the threat toxins.

It is unlikely that chemical synthesis of complex nonprotein toxins will become significantly easier in the near future. It is likely, however, that large-scale biosynthesis of peptide toxins of 10-15 amino acids (some of the venom toxins) will become possible in the next few years.

I have attempted to present a rationale for focusing our medical biological defense resources on the development of medical countermeasures for those toxins that our soldiers are most likely to face on the battlefield in the next 5 years. We must also continue limited basic research efforts and maintain "technical watch" of the peptide and other toxins that could become the

next generation of toxin weapons. Medical defense against biological weapons requires constant vigilance, especially today, because biotechnology is now available worldwide.

COUNTERMEASURES TO TOXINS

Although the threat of toxin weapons of the future is formidable, the prospect of new and better medical countermeasures is brighter than ever before. Biotechnology may have more value to those of us developing countermeasures than to those who would use toxins maliciously. Molecular biological techniques developed in the last few years now allow us to produce more effective and less expensive vaccines against the protein and peptide toxins. Such vaccines will likely be available for the most important toxins within the next few years. We are making good progress on developing recombinant vaccines for certain high-threat toxins. Similar technology allows us to produce human antibodies, which will eventually replace those now produced in animals. Human antibodies will be a significant advance over despeciated horse antibodies, allowing us to protect unvaccinated soldiers by simply giving them an injection before they go into battle, thereby providing immediate protection. Human antibodies could also find application in counterterrorism as therapy.

PROTECTING SOLDIERS

Protecting soldiers on the battlefield from toxins—and replicating agents—is possible if we use our combined resources effectively. Physical countermeasures such as the protective mask, clothing and decontamination capabilities exist and are effective; as we improve our battlefield detection systems, early warning of our soldiers may become a reality, at least in subpopulations within our forces. These assets, unlike most medical countermeasures, are generally generic and protect against most or all of the agents. Among the medical countermeasures, vaccines are available and effective for some of the most important agents and therapies exist for others. Because of limited resources available to develop vaccines, diagnostics and therapies, we can field specific medical countermeasures only to a relatively small group of threat agents. Our efforts in this area must be carefully focused. A third and complementary element of our defensive program must be good intelligence. Only through knowledge of specific threat agents, delivery systems, and national capabilities can we assure effective development and use of our physical and medical countermeasures.

Finally, our renewed understanding of the real strengths and weaknesses of toxins as weapons allows us to put them in perspective in educating our soldiers, removing much of the mystique—and associated fear—surrounding toxins. Knowledge of the threat thus reduces the threat to our soldiers.

TABLE 2: COMPARATIVE LETHALITY OF SELECTED TOXINS AND CHEMICAL AGENTS IN LABORATORY MICE

AGENT	LD_{50} (µg/kg)		MOLECULAR WEIGHT	SOURCE
Botulinum Toxin	0.001		150,000	Bacterium
Shiga Toxin	0.002		55,000	Bacterium
Tetanus Toxin	0.002		150,000	Bacterium
Abrin	0.04		65,000	Plant (Rosary Pea)
Diphtheria Toxin	0.10		62,000	Bacterium
Maitotoxin	0.10		3,400	Marine Dinoflagellate
Palytoxin	0.15		2,700	Marine Soft Coral
Ciguatoxin	0.40		1,000	Fish/Marine Dinoflagellate
Textilotoxin	0.60		80,000	Elapid Snake
C. perfringens toxins	0.1-5.0		35,000-40,000	Bacterium
Batrachotoxin	2.0		539	Arrow-Poison Frog
Ricin	3.0		64,000	Plant (Castor Bean)
α-Conotoxin	5.0		1,500	Cone Snail
Taipoxin	5.0		46,000	Elapid Snake
Tetrodotoxin	8.0		319	Puffer Fish
α-Tityustoxin	9.0		8,000	Scorpion
Saxitoxin	10.0	(Inhal; 2.0)	299	Marine Dinoflagellate
VX	15.0		267	Chemical Agent
SEB (Rhesus/Aerosol)	27.0	(ED_{50}-pg)	28,494	Bacterium
Anatoxin-A(s)	50.0		500	Blue-Green Alga
Microcystin	50.0		994	Blue-Green Alga
Soman (GD)	64.0		182	Chemical Agent
Sarin (GB)	100.0		140	Chemical Agent
Aconitine	100.0		647	Plant (Monkshood)
T-2 Toxin	1,210.0		466	Fungal Mycotoxin

TABLE 4: Differential Diagnosis of Chemical Nerve Agent, Botulinum toxin and Staphylococcal Enterotoxin B Intoxication.

	Chemical Nerve Agent	Botulinum Toxin	Staphylococcal Enterotoxin B
Time to Symptoms	Minutes	Hours (24-72)	Hours (1-6)
Nervous	Convulsions, muscle twitching	Progressive paralysis	Headache Muscle aches
Cardiovascular	Slow heart rate	Normal rate	Normal or Rapid Heart Rate
Respiratory	Difficult breathing, airways constriction	Normal, then progressive paralysis	Nonproductive cough Severe cases; chest pain/difficult breathing
Gastrointestinal	Increased motility, pain, diarrhea	Decreased motility	Nausea, vomiting and/or diarrhea
Ocular	Small pupils	Droopy eyelids	May see "red eyes" (conjuntival injection)
Salivary	Profuse, watery saliva	Normal, but swallowing difficult	May be slightly increased quantities of saliva
Death	Minutes	2-3 days	Unlikely
Response to Atropine/2PAM-Cl	Yes	No	Atropine may reduce gastrointestinal symptoms

About the author...

Colonel David R. Franz, Deputy Commander of the U.S. Army Medical Research Institute of Infectious Diseases, has served within the Medical Research and Development Command for 19 of his 23 years on active duty. He has been assigned to four of the Command's laboratories and has personally conducted research and published in the areas of frostbite pathogenesis, organophosphate chemical warfare agent effects on pulmonary and upper airways function, the role of cell-mediated small vessel dysfunction in cerebral malaria, and most recently, medical countermeasures to the biological toxins. Before joining the Command, he served as Group Veterinarian for the 10th Special Forces Group. Recently Colonel Franz has served as Chief Inspector on two United Nations Special Commission biological warfare inspection missions to Iraq and as technical advisor on long-term monitoring. He also served as a member of the first two US/UK teams which visited Russia in support of the Trilateral Joint Statement on Biological Weapons and as a member of the Trilateral Experts' Committee for BW negotiations. Colonel Franz holds the D.V.M. degree from Kansas State University and the Ph.D. in Physiology from Baylor College of Medicine.