REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
2005	open literature publication – book chapter	

4. TITLE AND SUBTITLE

Bio Warfare and Terrorism: Toxins and Other Mid-Spectrum Agents

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Madsen, JM

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

US Army Medical Research Institute of Chemical Defense
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Aberdeen Proving Ground, MD 21010-5400

8. PERFORMING ORGANIZATION REPORT NUMBER

USAMRICD-P05-027

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

US Army Medical Research Institute of Institute of Chemical Defense
ATTN: MCMR-CDA-T
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Aberdeen Proving Ground, MD 21010-5400

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

Published in Encyclopedia of Toxicology, 2nd edition (ed. P. Wexler). Academic Press, 273-279, 2005.

14. ABSTRACT

15. SUBJECT TERMS

Biowarfare, toxins, terrorism

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			James M. Madsen
UNLIMITED	UNLIMITED	UNLIMITED	UNLIMITED	7	19b. TELEPHONE NUMBER *(include area code)* 410-436-2230

Bio Warfare and Terrorism: Toxins and Other Mid-Spectrum Agents

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Published by Elsevier Inc.

Introduction and Classification

Toxins are toxic chemicals that can be elaborated by a biological organism. The word 'toxin' is often loosely used to mean poison but should be reserved for its more restricted definition; toxicant is a better synonym for poison. Several of the less complex toxins can now be synthesized in the laboratory or produced by other organisms following gene insertion, but synthetic toxins identical to their naturally occurring counterparts are still by definition toxins. Related terms include phycotoxins (toxins from algae), mycotoxins (fungal toxins), phytotoxins (plant toxins), and venoms (toxins from animals, especially vertebrates). Endotoxins are lipopolysaccharide toxins in the cell walls of certain gram-negative bacteria, and enterotoxins are toxins, such as cholera toxin, that damage intestinal mucosal cells. An exotoxin is a toxin that an organism releases into the environment. The actual toxin secreted by cells has in some cases been altered from the protoxin initially formed within the cells. Toxins usually do not perform crucial metabolic functions within their organisms of origin but act as offensive or defensive reactions to other organisms.

More than 400 toxins are known. They may be grouped according to size: low-molecular weight (LMW) toxins, which may be either peptides or nonpeptide organic compounds such as domoic acid, weigh less than 1 kDa and, if peptides, have no more than ~10 amino acids; heavier (larger) toxins are called protein toxins. Classification by organism of origin leads to the division of toxins into bacterial, algal, fungal, plant, marine dinoflagellate, marine soft coral, arthropod, molluscan, and vertebrate toxins. Toxins of similar chemical structure can be grouped together. Pathophysiologically, toxins comprise at least three major groups depending upon their toxicodynamics, or mechanisms of action. Neurotoxins, which affect neurotransmission, include botulinum toxin (which blocks the release of acetylcholine from cholinergic neurons), anatoxin, saxitoxin, and many animal venoms, some of which act presynaptically and others of which act postsynaptically. Membrane-damaging toxins include ricin, microcystin (which is also a hepatotoxin), certain venoms (such as the hemolytic snake venoms), and the trichothecene mycotoxins. Superantigen toxins such as staphylococcal enterotoxin B, toxic shock syndrome toxin-1, and streptococcal pyrogenic exotoxins exert pronounced systemic effects by activating the immune system in a nonspecific way.

Bioregulators are potent low-molecular peptides and proteins that modulate a wide variety of physiological processes such as inflammation, blood clotting, and neurotransmission. Unlike most toxins, they have definite roles in the normal physiology of their hosts. Bioregulators are not normally considered poisons but at toxicological doses may produce dramatic effects on blood pressure, body temperature, and other physiological parameters.

As chemicals produced by biological organisms, toxins and bioregulators occupy a zone that lies between chemical and biological agents and overlaps them to some extent. Saxitoxin and ricin are listed as chemical agents in the Chemical Weapons Convention, and toxins are listed separately from biological agents in the Biological and Toxin Weapons Convention (BTWC). The usual practice is to group toxins with biological agents. This is natural and appropriate from the perspectives of production, storage, and treaty issues, since toxins are generally produced by and often stored near their biological agents of origin. However, from a clinical standpoint, both toxins and bioregulators resemble other chemicals in that they do not replicate inside their hosts, are not transmissible, and are amenable to a chemical-based approach to clinical management. The term mid-spectrum agents (or mid-spectrum chemical warfare agents) has been proposed to refer to toxins and bioregulators along with synthetic viruses and genocidal agents produced by recent advances in biotechnology. **Table 1** displays one classification scheme for these compounds; the agents that are underlined will receive particular attention in this entry. Agents discussed as separate entries in this encyclopedia are also so indicated.

History

For millennia, indigenous South Americans deliberately used plant-derived arrow poisons such as curare and also toxins from poison-dart frogs, although these preparations were used mainly for hunting; similar toxins were used in Africa. The military use

*The conclusions and opinions expressed in this document are those of the author and do not necessarily reflect the official position of the United States Government, the Department of Defense, the United States Army Medical Research Institute of Chemical Defense, or the Uniformed Services University of the Health Sciences.

Table 1 Toxins and other mid-spectrum agents relevant to warfare and terrorism: a classification scheme

TOXINS
Bacterial toxins
Phycotoxins (algal toxins)
Botulinum toxin (CDC Category A)
Epsilon toxin from *Clostridium perfringens* (CDC Category B)
Staphylococcal enterotoxin B (SEB) (CDC Category B)
Diphtheria toxin
Tetanus toxin
Shigatoxin (veratoxin)
Mycotoxins (fungal toxins)
Aflatoxins
Ergot alkaloids (historical)
Trichothecene mycotoxins
  Stachybotrotoxins, including satratoxin H
  T-2 mycotoxins
Marine toxins
Phycotoxins (algal toxins)
  Algal toxins (blue-green algal) toxins
    Anatoxin-A (AnTx-a)
    Microcystins and nodularins
    Saxitoxins (STX), causing paralytic shellfish poisoning (PSP)
  Diatom toxin
    Domoic acid, causing amnesic shellfish poisoning (ASP)
  Dinoflagellate toxins
    Brevetoxins (PbTx), causing neurotoxic shellfish poisoning (NSP)
    Ciguatoxins (CTX) and maitotoxins (MTX), causing ciguateric fish poisoning (CFP)
    Diarrheic shellfish toxins (DST), causing diarrheic shellfish poisoning (DSP)
     Okadaic acid
    Palytoxin (concentrated by corals)
Conotoxins (from cone snails)
Scombrotoxins (mainly histamine)
Tetrodotoxin (TTX)
Phytotoxins (plant toxins)
(numerous alkaloids, including curare)
Type 2 ribosomal-inhibitory-protein (RIP) toxins
  Ricin (CDC Category B)
  Abrin
  Eranthis hyemalis lectin (EHL) from winter aconite
  Modeccin
  Viscumin
  Volkensin
Venoms from land animals
Invertebrate toxins, mostly from arthropods
Vertebrate toxins
  Amphibian toxins, including batrachotoxin
  Snake and lizard venoms
  Bird toxins (mainly batrachotoxin)

BIOREGULATORS
Cytokines
Early-phase proinflammatory cytokines (endogenous pyrogens)
  Interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α)
  IL-6
  IL-18
  Interferon gamma (IFN-γ)
Chemokines
  IL-8

Table 1 Continued

Eicosanoids (prostanoids and leukotrienes)
Prostaglandin D_2 (PGD_2), leukotrienes C_4 (LTC_4), LTD_4, LTE_4
LTB_4
Neurotransmitters and hormones
Catecholamines (e.g., epinephrine, norepinephrine, serotonin, dopamine)
Amino acid neurotransmitters (e.g., glutamate, aspartate, glycine, and γ-aminobutyric acid, or GABA)
Neuropeptides
  Neuropeptide Y
  Opioids (endorphins and enkephalins)
  Tachykinins
    Neurokinins A and B
    Substance P
Insulin
Vasopressin
Cholecystokinin
Somatostatin
Neurotensin
Bombesin
Vasoactive plasma proteases
Kallikreins and bradykinins
Tissue factor and thrombin

SYNTHETIC VIRUSES
Poliovirus
Other viruses identical to their natural counterparts
Genetically modified or combined synthetic viruses

GENOCIDAL AGENTS
Toxins, bioregulators, synthetic viruses, or traditional agents modified to enhance virulence
Toxins, bioregulators, synthetic viruses, or traditional agents modified to target specific genotypes

of toxins dates from at least the sixth century BC, when Assyrian soldiers poisoned enemy wells with ergot-contaminated rye. The ancient Greeks, for whom *toxikon* meant 'arrow poison', tipped arrows with aconite, and this practice continued into medieval Europe and persisted into the seventeenth century in Spain and Portugal. Japanese scientists in the infamous Unit 731 investigated tetrodotoxin during World War II, and suspicions have surfaced that the bomb used in the assassination of Reinhard Heydrich in Czechoslovakia in 1942 contained botulinum toxin. After World War II, ricin saw use as an injectable assassination weapon. More recently, Iraq had a weapons program that included the development of botulinum toxin, epsilon toxin from *Clostridium perfringens*, and aflatoxin. Militia groups in the United States and terrorist groups throughout the world have used ricin for political purposes. Toxins could be used on the battlefield or by terrorists to generate large numbers of military or civilian casualties as a mass-casualty weapon (MCW), to spread panic, for assassinations, or, in the case of toxins that damage crops, to create damage to an economy.

Concepts Relevant to Military or Terrorist Use

Toxicity

Toxins include several of the most acutely toxic chemicals known. For example, botulinum toxin is generally conceded to be the most lethal poison in existence. However, agent toxicity by itself is only a beginning variable that is subsequently modified by environmental and host factors. Because most toxins are far less toxic than botulinum toxin, tons of those toxins may be needed to cover a desired area on the battlefield. Many groups of toxins can thus be assumed to be at low risk of use as mass casualty weapons, or MCWs (but not necessarily as tools of assassins or for terrorist use in buildings), simply because of their relatively low toxicities. Others can be excluded on the basis of difficulties with isolation, synthesis (in general, chemical synthesis of only selected LMW toxins is currently feasible), production, storage, or dissemination; and still others degrade too rapidly in the environment. In general, the highest toxicities (lowest LD_{50} values, or lethal doses for 50% of a group) are associated with high-molecular weight (HMW) bacterial toxins such as botulinum toxin (MW 150 000 Da; LD_{50} 0.001 $\mu g\,kg^{-1}$), tetanus toxins (MW 150 000 Da; LD_{50} 0.002 $\mu g\,kg^{-1}$), and shigatoxin (MW 55 000 Da; LD_{50} 0.002 $\mu g\,kg^{-1}$). On the other end of the scale, aconitine (MW 647 Da; LD_{50} 100 $\mu g\,kg^{-1}$) is of the same order of toxicity as the nerve agent sarin; and T-2 mycotoxin (MW 466 Da; LD_{50} 1210 $\mu g\,kg^{-1}$) is approximately as toxic as the vesicating chemical agent sulfur mustard. Nonetheless, exceptions do occur; and the potency of a given toxin depends not only upon its size and structure but also upon its formulation (e.g., particle size in an aerosol) and, notably for most toxins, upon the route of entry.

States in the Environment and Routes of Entry

Although toxins do not volatilize as do many (but not all) chemical agents, this difference is moot as long as aerosolized toxin is capable of being inhaled. The preferred mode of dissemination for toxins used as MCWs would usually be the generation of appropriately sized particles in an aerosol, and the most pertinent route of exposure would be inhalation during the initial dispersion of agent. Primary aerosolization and inhalation have been conclusively demonstrated to be practical for botulinum toxin, staphylococcal enterotoxin B, ricin, T-2 mycotoxin, aflatoxins, brevetoxins (naturally, from wave-induced sprays of algal blooms), domoic acid, saxitoxin, tetrodotoxin, and others. Once an agent has settled onto environmental surfaces, its ability to reaerosolize largely determines its likelihood for subsequent inhalation. This property varies from toxin to toxin and from formulation to formulation and also depends upon environmental conditions such as humidity and temperature. Secondary aerosolization is presumed to be negligible for many toxins, but this assertion has not been rigorously demonstrated for all of these compounds. Many toxins are stable for long periods on environmental surfaces and in water; trichothecene mycotoxins and palytoxin are particularly persistent, but even botulinum toxin can remain in nonmoving water and in food for weeks. Personnel decontamination can usually be accomplished by gentle flushing using water with or without soap.

Most toxins are neither absorbed through intact skin nor dermally active, but there are exceptions, to include T-2 mycotoxin, lyngbyatoxin, and other blue-green algal toxins (cyanobacterial toxins). Ricin and abrin are among toxins that may incite an allergic contact response. Certain toxins and certain bioregulators, especially if heavily glycosylated, can survive ingestion to be absorbed from the gastrointestinal tract, and parenteral absorption of injected ricin was responsible for the death of Bulgarian dissident Georgi Markov in London in 1978 and was suspected in several other assassinations. This kind of attack, depending upon surreptitious employment of an umbrella modified to inject a ricin-filled pellet, would appear to be more suited to isolated assassinations than to use as a mass casualty weapon, but saxitoxin, which is particularly stable even under high temperatures, has been considered for coating bullets.

Threat Estimates

Risk assessment of possible use of toxins and related mid-spectrum agents on the battlefield or as terror weapons is an inexact science at best. Even if a toxin or a bioregulator is extremely potent, it may not be easily weaponizable, it may not survive long in the environment (particularly for bioregulators), or it may be so rare that the resources required to isolate it from natural sources or (in the case of LMW compounds) to synthesize it would be prohibitive. However, a determined individual, terrorist cell, or state with available time, personnel, equipment, and natural product may overcome these limitations, particularly if the goal is to use a little-known agent that will be low on the list of differential diagnoses for the effects produced. The rapid development of new techniques in biotechnology, toxicogenomics, and proteomics may also help to open the door to the

production, storage, and dissemination of exotic mid-spectrum agents. The Centers for Disease Control and Prevention (CDC) in the United States has established three threat categories for biological agents and toxins; botulinum toxin appears in category A (the highest-threat group), and ricin, epsilon toxin from C. *perfringens*, and staphylococcal enterotoxin B (SEB) all reside in category B. Abrin does not appear on the list, perhaps because it is less readily available than ricin. However, its toxicity is almost an order of magnitude higher than that of ricin. T-2 mycotoxin is asserted to have been used in Southeast Asia from 1975 to 1981, and despite continuing controversy regarding these claims, its potential for use appears to be significant despite its absence from the CDC list. Iraq stockpiled aflatoxin at one point for possible use, and saxitoxin, domoic acid, and tetrodotoxin have been mentioned as toxins capable of weaponization as MCWs. It seems safe to assert that although the most likely toxins to be used in warfare or terrorism include botulinum toxin, ricin, staphylococcal enterotoxin B, and perhaps trichothecene mycotoxins, all of which have been seriously investigated for military use, several other candidates exist and should not be excluded from consideration. The likelihood of development and use of bioregulators, synthetic viruses, and genocidal agents is even less predictable but should be expected to rise with new advances in biotechnology. Space prohibits discussion of each of the agents in **Table 1**, but a brief overview of each of the underlined toxins in **Table 1** will be presented.

Representative Agents

Botulinum Toxin

Chemical Abstracts Service Registry Number: CAS 93384-43-1. Botulinum toxins comprise a series of seven related protein neurotoxins that prevent fusion of synaptic vesicles with the presynaptic membrane and thus prevent release of acetylcholine. Exposure in a battlefield or terrorist setting would most likely be to inhaled aerosolized toxin. The clinical presentation is that of classical botulism, with descending skeletal muscle weakness (with an intact sensorium) progressing to respiratory paralysis. A toxoid vaccine is available for prophylaxis, and a pentavalent toxoid can be used following exposure; its effectiveness wanes rapidly, however, after the end of the clinically asymptomatic latent period. Because treatment is supportive and intensive (involving long-term ventilatory support), the use of botulinum toxin has the potential to overwhelm medical resources especially at forward echelons of care.

Ricin

Chemical Abstracts Service Registry Number: CAS 9009-86-3. Ricin, easily extracted from the castor bean plant (*R. communis*), is a globular glycoprotein membrane-damaging toxin with an A chain and a B chain separated by a disulfide bond. The A chain binds to the 28S unit of ribosomes to impair protein synthesis. The clinical presentation is very much dependent upon the route of entry: ingestion produces predominantly gastrointestinal effects, inhalation causes airway necrosis and damage to alveolar-capillary membranes leading to diffuse necrotizing pneumonitis and pulmonary edema, and parenteral exposure (from injection or from contamination of wounds) generally spares the respiratory tract but leads to necrosis of lymph nodes, gastrointestinal mucosa, the liver, the kidneys, and the spleen and to disseminated intravascular coagulation. Local cutaneous reactions and absorption may also follow contact with intact skin. The results of active prophylaxis with toxoid have been encouraging in animal studies, but treatment in humans remains empirical and supportive.

Abrin

Chemical Abstracts Service Registry Number: CAS 1393-62-0. Abrin is a toxalbumin similar in structure, absorption, and mechanism of action to ricin but is found not in castor beans but rather in jequirity beans. No reports of its use as a battlefield or terrorist agent exist, but in mice it is 75 times more potent than ricin. No specific treatment is available. Both ricin and abrin are type 2 ribosomal inhibitory proteins (RIPs): the other potent toxins in this class are *Eranthis hyemalis* lectin (EHL) from winter aconite, modeccin and volkensin from African succulents, and viscumin from mistletoe.

Epsilon Toxin from *Clostridium perfringens*

Clostridium perfringens has at least six serotypes and produces over 20 toxins. Epsilon toxin, along with alpha, beta, and iota toxins, is dermonecrotic and lethal. It is produced by some strains of type B and especially type D as a protoxin that is then converted to an active, mature, heat-labile toxin. The resulting toxin binds to cell membranes and forms a membrane complex that promotes the efflux of intracellular potassium. Because the usual route of entry is the gastrointestinal tract, the resulting pathology is an increase in intestinal permeability that enhances absorption of more toxin and ensures systemic toxemia. In animals, increased vascular permeability leads to enterotoxemia, 'pulpy kidney', altered hepatic function, and cerebral edema and necrosis.

Aerosolized alpha toxin from *C. perfringens* causes serious pulmonary damage with vascular leakage, hemolysis, thrombocytopenia, and liver damage and could easily be lethal, but the effects in humans of epsilon toxin, especially from inhalation, are unclear. However, the Iraqi biological agent program included the study not only of *Bacillus anthracis* and *Clostridium botulinum* but also of *C. perfringens*, including its epsilon toxin. Theoretically, this toxin could be genetically combined with another agent to increase the absorption of both. Animal toxoids exist but have not been evaluated for safety or efficacy in humans.

Staphylococcal Enterotoxin B (SEB)

Chemical Abstracts Service Registry Number: CAS 11100-45-1. SEB, the toxin that after ingestion causes sudden-onset staphylococcal food poisoning, is one of seven enterotoxins elaborated by *Staphylococcus aureus*. It is resistant to both heat and freezing. As a superantigen toxin, its mechanism of action involves binding to receptors for T-cell antigens and to major histocompatibility complex class II molecules, bypassing normal routes for antigen recognition and leading to antigen-nonspecific activation of the immune system and a massive release of bioregulatory cytokines to include not only histamine and leukotrienes (responsible for the intestinal response) but also interferon gamma, interleukin-6, and tumor necrosis factor alpha (responsible for systemic effects). Inhalation of aerosolized SEB leads to incapacitating respiratory signs and symptoms, although deaths at high doses may occur from pulmonary edema. Inadvertently swallowed toxin may also produce nausea and vomiting.

In a military or a terrorist setting, SEB could be added to unguarded food or water or could be disseminated by aerosol. The resulting incapacitation may be a desirable goal either on the battlefield or for terrorism. Human trials of a pre-exposure toxoid and of post-exposure passive immunization are underway but have not yet led to approved products.

T-2 Mycotoxin

Chemical Abstracts Service Registry Number: CAS 21259-20-1. T-2 mycotoxin is a trichothecene toxin, so-called because of two particular chemical moieties in its structure. Many otherwise unrelated groups of fungi produce a rich variety of trichothecene mycotoxins, each with its own toxicological profile. T-2 mycotoxin has been associated with disease in animals and, in the 1930s in the Soviet Union, with a largely gastrointestinal condition called alimentary toxic aleukia, a chronic intoxication from repeated consumption of contaminated bread. This toxin was also found in autopsy specimens from one of the Khmer Rouge casualties associated with the yellow, green, red, or white smoke that came to be called yellow rain in Laos and Cambodia (now Kampuchea) in the 1970s. Whether the T-2 toxin acted in concert with other mycotoxins found in the victim and to what extent it was responsible for the observed results remain matters of controversy, even though laboratory exposures to the toxin created similar cutaneous, ocular, and systemic effects. The toxicity of T-2 mycotoxin, which is also one of the few toxins capable of creating small vesicles on the skin after direct contact, is roughly comparable to that of the chemical agent sulfur mustard, and relatively large quantities would be needed to cause casualties over a large area. The cytotoxicity of T-2 toxin is thought to be related to lipid peroxidation of plasma membranes, inhibition of electron (proton) transport in mitochondria, and especially RNA inhibition and consequent disruption of protein synthesis in ribosomes. Treatment is supportive, supplemented with steroids.

Aflatoxin

Chemical Abstracts Service Registry Number: CAS 1402-68-2. Aflatoxins are toxic, immunosuppressive, mutagenic, and carcinogenic mycotoxins produced by the mold *Aspergillus flavus* and commonly contaminating cereals, oilseeds, tree nuts, and spices. They are quite resistant to dry heat but gradually deteriorate under conditions of moist heat. They are also inactivated by food additives such as sodium bisulfite. Aflatoxin was first recognized as a toxin for animals following a severe outbreak of 'Turkey X' disease in the United Kingdom in 1960. Since that time, outbreaks of human disease have been reported, including one from contaminated maize in Kenya during May 2004; the case fatality rate for this outbreak approached 50% in one of the affected districts. Iraq is known to have included aflatoxin in its arsenal; it is unclear whether this toxin was intended to be used to cause acute effects or to cause cancer years later in survivors (or both) is unclear. In the body, cytochrome P450 converts the toxin (usually after ingestion) to an epoxide that reacts with RNA and DNA, inhibits protein and DNA synthesis in the liver and bone marrow, and can lead to mutations and eventually cancer. The acute clinical manifestations are protean and include vomiting, abdominal pain, gastrointestinal hemorrhage, fatty change of the liver, pulmonary edema, convulsions, and cerebral edema; chronic effects include liver cancer. Treatment is supportive.

Domoic Acid

Chemical Abstracts Service Registry Number: CAS 14277-97-5. Domoic acid, a glutamic acid analog that is resistant to temperature extremes, is an excitatory neurotoxin produced by a diatom and concentrated in shellfish. Ingestion leads to amnesic shellfish poisoning, which can also include seizures. Its relevance to use in warfare and terrorism, apart from its being unfamiliar to most disaster-response personnel, is that it is also easily absorbed by inhalation and across mucous membranes. No specific antitoxin is available, and treatment is supportive.

Saxitoxin (STX)

Chemical Abstracts Service Registry Number: CAS 35523-89-8. Saxitoxin, a heat-stable neurotoxin produced by blue-green algae, is associated with paralytic shellfish poisoning. It leads to weakness and paralysis by blocking sodium channels in neurons. It is a potential agent for use on the battlefield or in terrorism because of its increased potency via inhalation, its fast onset and progression, and its proposed use for coating projectiles such as bullets. No toxoid or antitoxin is available.

Tetrodotoxin (TTX)

Chemical Abstracts Service Registry Number: CAS 4368-28-9. Tetrodotoxin, a neurotoxin produced by several species of starfish, crabs, salt-water fish, octopi, newts, and salamanders, blocks sodium channels within neurons. In a terrorist scenario, tetrodotoxin could be inhaled as an aerosol or ingested in contaminated food or water. Mortality may reach 50%.

Bioregulators

All of the bioregulators listed in **Table 1** are potentially weaponizable, although not all with present-day technology. Their attractiveness as weapons of assassination or to produce mass casualties is tied to several possible advantages. They are not on most standard lists of agents to be expected in warfare or terrorism, they are easily purchased (partly because they are used extensively in research), they are rapid in onset (making them useful assassination agents) but relatively nonspecific in their clinical effects (thus not arousing suspicion), and no vaccines are available against them. However, the costs of production or purchase may be high, they may not be available in large enough quantities to be effective, and neither their aerosolizability nor their environmental persistence has been characterized thoroughly. Nevertheless, since enteral absorption is significant for many of these compounds, they could also be added to foodstuffs.

Synthetic Viruses

Simple viruses such as the polio virus, consisting of a single strand of RNA, have already been successfully assembled using commercially available reagents. Larger and more complex viruses will undoubtedly be synthesized in the near future, and the relative ease with which this can be done, and the possibility of designing and testing novel viral structures not found in nature, could lead to large quantities of completely new agents. Since these compounds can be synthesized in a laboratory setting but can then replicate within hosts, they are prototypical mid-spectrum agents.

Genotoxic Agents

The ability to synthesize viral genomes is part of the burgeoning development of biotechnology, which uses high-speed data processing, microarrays, and the new sciences of genomics and proteomics to alter genetic code and to affect the expression of that code. Bioengineered viruses and other organisms could be targeted toward individuals or populations with specific genotypes. Toxicogenomics could be used in a similar way for chemical agents and for mid-spectrum agents such as toxins and bioregulators.

Summary

Toxins, which are chemical poisons produced by living organisms, and bioregulators, which are LMW molecules involved in physiological processes within the body, are biological in origin but are noninfectious and nonreplicating. As mid-spectrum agents, they occupy a position between and overlap the traditional dichotomy of mass-casualty agents as chemical versus biological agents. This part of the spectrum may also be said to include synthetic viruses and genotoxic agents. All of the mid-spectrum agents have potential for use in small-scale or large-scale operations against military forces, civilians, or both. An appreciation of the unique position of these agents and of the threat that they pose and a heightened level of suspicion for their use are necessary in order to recognize their use and institute appropriate preventive and treatment measures.

See also: Aflatoxin; Algae; Botulinum Toxin; Castor Bean; Ciguatoxin; *Clostridium perfringens*; Marine Organisms;

Mold; Mycotoxins; Ricin and Other Toxalbumins; Saxitoxin; Scombroid; *Staphylococcus aureus*; Tetrodotoxin.

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Biocides

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:l.10052

Published by Elsevier Inc.

The word 'biocide' encompasses a broad class of chemical agents and literally means an agent that destroys life. The United States Environmental Protection Agency defines the term 'biocide' as follows:

> A diverse group of poisonous substances including preservatives, insecticides, disinfectants, and pesticides used for the control of organisms that are harmful to human or animal health or that cause damage to natural or manufactured products.

This broad definition includes terms and topics covered in this encyclopedia and other literature, including pesticides, which encompasses herbicides, insecticides, miticides, rodenticides, algaecides, etc. Biocides have sometimes been considered a subcategory of pesticides. When the term is used in this context, it refers specifically to the control or destruction (killing) of microorganisms, typically in nonagricultural applications. Biocides as nonagricultural pesticides encompass a wide range of applications, including disinfectants and sanitizers, preservatives and microbicides, antifouling products, wood preservatives, and structural treatments.

Biocides are used widely in industry. There are at least three main classes of industrial chemical biocides. The first class includes the oxidizing and bleaching agents, such as chlorine dioxide, hydrogen peroxide, and sodium hypochlorite. The oxidizing action may directly kill bacteria or fungi or weaken the cell walls so that they are more susceptible to other classes of biocides (see below). Sodium hypochlorite (like all hypochlorites) is a salt of hypochlorous acid. In solution, it splits into the sodium cation (Na^+) and the hypochlorite anion (ClO^-). The oxidizing power of the latter causes the bleaching and disinfecting effect. Chemicals with oxidizing and bleaching properties have been under scrutiny in recent years. This is largely because of the toxicity of reaction by-products, particularly chlorine and its derivatives. There is a high probability of the formation of toxic gases (chloramine gas) and mutagenic and/or carcinogenic halogen-containing organic substances (e.g., trihalomethanes) during water treatment activities and when these chlorine-containing compounds are released into the environment. As a result, there has been an increase in the use of oxygen, hydrogen peroxide, and other oxygenated compounds in bleaching applications, and a sharp decline in the demand for chlorine and the hypochlorites.

A second class of industrial chemical biocides involves highly toxic organic chemicals. Subclasses of toxic biocides include thiazoles, thiocyanates, isothiazolins, cyanobutane, dithiocarbamate, thione, and bromo-compounds. As the names imply, many of the toxic biocides contain sulfur ('thio'-).

A third class of industrial chemical biocides consists of agents with the ability to inhibit biological film formation, also called 'surfactants'. The term surfactant originates from the phrase surface active agent. Surfactants fall into four broad categories: anionic (e.g., soaps, alkyl benzenesulfonates, alkyl sulfonates, alkyl phosphates), cationic (e.g., quaternary ammonium salts), nonionic (e.g., alkyl polyglycosides, alcohol ethoxylates, alkylphenol ethoxylates), and zwitterionic.