

Toxins as Weapons: A Historical Review

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ABSTRACT: This review article summarizes the use of toxins as weapons dating from the First World War until today, when there is a high concern of possible terrorist attacks with weapons of mass destruction. All through modern history, military programs and terrorist groups have favored toxins because of their high toxicity. However, difficulties of extraction or synthesis, as well as effective dissemination to cause a large number of casualties, have been the most important drawbacks. Special emphasis is focused on ricin and botulinum toxin, the most important toxins that have attracted the attention of military programs and terrorist groups. Other toxins like trichothecenes, saxitoxin, and Staphylococcal enterotoxin B (SEB) are also discussed. A short section about anthrax is also included: Although *Bacillus anthracis* is considered a biological weapon rather than a toxin weapon, it produces a toxin that is finally responsible for the anthrax disease.

KEY WORDS: Bioterrorism, botulinum toxin, ricin, toxin weapons.

INTRODUCTION

Toxins are chemical substances of biological origin, and can be considered chemical or biological warfare agents. In fact, toxins are covered in the Chemical Weapons Convention (CWC), as it deals with toxic chemicals “regardless of their origin or of their method of production”, but also in the Biological and Toxin Weapons Convention (BTWC). For this reason, toxins are also called midspectrum agents.

The US Army Medical Research Institute of Infectious Diseases (USAMRIID) considers that botulinum toxin, ricin, Staphylococcal enterotoxin B (SEB) and T-2 trichothecene are the most likely to be used as weapons (**Table 1**) [73]. Nearly all toxins developed as weapons are nonvolatile solids at room temperature and produce their toxicological effects when inhaled [16]. Therefore, the best weaponization would be obtained by the dissemination of an aerosol with a particle size of 0.5–5µm, expressed as mass median aerodynamic diameter (MMAD), which favors alveoli retention and absorption [55]. This MMAD is also adequate to maintain particles in the air during an adequate period of time, increasing the probability of inhalation by the targeted enemy. While obtaining an adequate MMAD aerosol may not be an easy task, there have been other drawbacks to the use of toxins as weapons,

mainly their low stability and the difficulties of producing/extracting them in large quantities [48,49].

Four toxins are included in the list of what the US Centers for Disease Control and Prevention (CDC) considers bioterrorism agents: botulinum toxin, epsilon toxin of *Clostridium perfringens*, ricin, and SEB [74]. However, of these four toxins, only ricin and botulinum toxin have attracted the attention of terrorist groups. Botulinum toxin is included in Category A, while the other three are considered as Category B. Category A includes high-priority agents that pose a risk to national security because they:

- can be easily disseminated (or, in the case of infectious pathogens, easily transmitted from person to person);
- result in high mortality rates and have the potential for major public health impact;
- might cause public panic and social disruption; and
- require special action for public health preparedness.

Category B agents are those that:

- are moderately easy to disseminate;
- result in moderate morbidity rates and low mortality rates; and
- require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance.

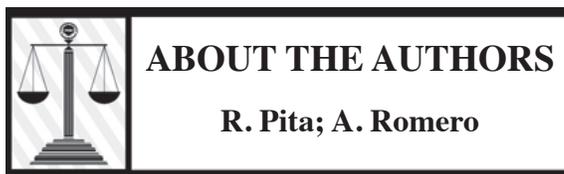
I. RICIN

A. Military Programs

Ricin is the toxin present in the castor plant (*Ricinus communis* L.), which is chemically stable and can be stored unrefrigerated for long periods of time with little loss of activity [44]. Although never used in combat, it was perhaps the first toxin studied as a weapon. As early as 1903, the US Army published a report describing how

Table 1. Toxins considered the most likely to be used as weapons

| Category | Name |
|----------------------|------------------------------------|
| Polypeptide toxin | Ricin |
| | Botulinum toxin |
| | Staphylococcal enterotoxin B (SEB) |
| Nonpolypeptide toxin | Trichothecenes |
| | Saxitoxin (STX) |



René Pita received his Ph.D. degree in neurotoxicology from Madrid Complutense University (Madrid, Spain) in 2005. He is currently a major in the Spanish Medical Corps and a professor at the Chemical Defense Department of the Spanish Army CBRN (Chemical, Biological, Radiological, and Nuclear) Defense School (Madrid, Spain).

Since 1995 Dr. Pita has been working in the CBRN defense field. He has extensive experience in the strategic, operational, and tactical aspects of CBRN defense, including many NATO and Proliferation Security Initiative (PSI) exercises. He has written extensively and given lectures on issues of CBRN terrorism. In 2007 Dr. Pita was selected as a qualified expert in toxicology by the Organisation for the Prohibition of Chemical Weapons (OPCW) — the implementing body of the Chemical Weapons Convention (The Hague, Netherlands) — for inspections of alleged use. He is currently a member of the Assistance and Protection Network of the OPCW.

Alejandro Romero graduated from the University of Vigo (Vigo, Galicia, Spain) in 2000 and obtained his Ph.D. degree in biological sciences from the same university in 2006 with an “Outstanding Doctorate Award”. Dr. Romero is currently an assistant professor at the Department of Toxicology and Pharmacology, Complutense University of Madrid (Madrid, Spain).

Dr. Romero started his doctoral study in 2002, with focus on neurotoxicology at the University of Vigo. In 2008, as a postdoctoral fellow, Dr. Romero joined Prof. Antonio G. García’s group at the Department of Pharmacology and Therapeutics, Autonomous University of Madrid (Madrid, Spain), where he was involved in neuroprotection studies. In 2010, he obtained the title of University Expert in Toxicology at the Sevilla Official College of Chemistry (Seville, Andalucía, Spain).

Dr. Romero’s current research is focused on neuroprotection studies and beneficial actions of melatonin in the central nervous system and related diseases. He has worked in 15 research projects, has made more than 80 presentations in national and international congresses, and has published more than 40 research articles in SCI journals.