



GLOBAL ISSUES

Toxin and Bioregulator Weapons

Preventing the Misuse of the
Chemical and Life Sciences

Michael Crowley
Malcolm R. Dando



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Global Issues

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The rapid pace of globalizing dynamics has brought in its wake a proliferation of crises, governance challenges and large-scale stresses, unprecedented in their range, seriousness and urgency. These emerging conditions and relations are variously global in their range, inclusiveness and impacts; and many of them are outpacing our legal, political and ethical systems of deliberation and control. Climate change, the ravages of contagious diseases and financial turmoil are all cases in point. Similarly, the transformative implications of new scientific and technological developments, from Big Data to gene editing, are already upon us. This book series is dedicated to providing insights into the complex interaction of human and natural systems; modes of cooperation and conflict; and the ways and degrees to which human values can be reconciled and more effectively enacted. The concentration throughout is on an integration of existing disciplines toward the clarification of political possibility as well as impending crises.

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Michael Crowley • Malcolm R. Dando

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Sciences

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*This book is dedicated to Julian Perry Robinson, a friend and mentor to us
and so many other people involved in preventing the development and use of
chemical and biological weapons*

FOREWORD

I have spent the bulk of my professional life working on efforts to uncover and destroy banned chemical and biological weapons. Michael Crowley and Malcolm R. Dando have written this extraordinarily timely and important book on toxin and bioregulator weapons, an often-overlooked area that exists in the overlap, or rather as the authors argue gap, between the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC).

The ongoing revolution in the life sciences, bioengineering, and the explosion in our understanding of the chemical processes that control us all is leading to incredible advances in medicine. The risks that these same beneficial new capabilities will be misused to develop even better and more precise toxin and bioregulator weapons, despite international conventions prohibiting them, are increasing.

Russia's vicious and unprovoked war against Ukraine is once again highlighting the fact that its use of such banned weapons of mass destruction is quite possible. The Chief of Russia's NBC Defense Forces General Igor Kirillov, who oversees three top secret suspected biological weapons laboratories in Kirov, Sergeev Posad and Yekaterinburg, has been spewing outrageous lies falsely accusing Ukrainian public health laboratories of developing biological weapons. These accusations raise the very real possibility that, as U.S. and U.K. intelligence have revealed, Russia may be planning to launch false flag attacks with these hideous weapons. Fast acting toxin and bioregulator weapons are among the most likely types Russia would use against Ukrainian forces and soft civilian targets.

This scholarly account of the impact of recent scientific advances on toxin and bioregulator weapons by two of the world's foremost experts on this topic will serve as an enduring textbook for scholars, scientists and diplomats alike.

The six country case studies, on China, India, Iran, Syria, Russia and the United States, make clear how hard it is to determine the intent behind dual-use research of concern. As the international community looks for ways to update and strengthen enforcement of the BTWC and CWC, this book will provide a valuable resource. It will also cause countries in compliance with treaty obligations to work harder to provide assurances to the world that there is no intent to develop banned weapons. Finally, diplomats should leverage this penetrating research to identify new ways to make it harder for countries to hide and deny efforts to develop these horrific weapons. As President Obama said, we must not let the worst weapons of the twentieth Century darken the twenty-first.

Senior Fellow, Council on Strategic Risks;
Former US Assistant Secretary of Defense
for Nuclear, Chemical and
Biological Defense Programs
Washington, DC, USA

Hon. Andy Weber

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We would like to thank Professor Kathryn Nixdorff, Dr Christopher Timperley, Dr Ralph Trapp, and Dr Jean Pascal Zanders for kindly reviewing some or all of our draft chapters and the two anonymous reviewers who commented on the whole draft script. Of course, any remaining errors are our responsibility. We would also like to thank the Omega Research Foundation and Gordon Arthur for giving permission to use their figures. Finally, we would like to acknowledge the Leverhulme Trust (EM-2018-005/10) for supporting Malcolm R. Dando.

Praise for *Toxin and Bioregulator Weapons*

“As advances in science teach us more about healthy human functioning, we inadvertently learn more about how these biological processes could potentially be disrupted to deliberately cause harm. How we can make sure this science is used for good, and not bad, is the topic of this important new book from internationally renowned experts Crowley and Dando. Focused specifically on toxins and bioregulators and how these chemical compounds can affect our nervous, endocrine and immune systems, the book presents a unique and timely body of work. Its collection of concrete examples from across the globe of research where the potential for weaponization and opportunities for repression are high, but the intent is unclear or could easily be misperceived, is unrivalled. In an age when artificial intelligence, big data, computational power and nanoscience converges with the life sciences, the potential for developing more precisely targeted, more capable and more accessible means to cause biological harm is increasing exponentially. A key question for our time is how the international community can raise political and legal barriers to states misusing life science advances. This book forms a substantial contribution to that debate.”

—Filippa Lentzos, *Senior Lecturer in Science & International Security*,
King's College London

“This book investigates the often-neglected issue of the regulation of mid-spectrum agents under the Biological and Toxin Weapons Convention and the Chemical Weapons Convention through the application of a standardised methodology to six country case studies: China, India, Iran, Russia, Syria and the United States. It reviews how we should think about preventing the misuse and promoting non-proliferation of chemical substances such as toxins and bioregulators that affect our physical life, and raises important issues within the framework of both the biological weapons prohibition and the chemical weapons prohibition. It also asks the key question of how should we respond to the current state of research and development in the life sciences? The book's approach to the dual-use nature of advanced life science research on chemicals is a must-read for all concerned.”

—Nariyoshi Shinomiya, *President of the National Defense*
Medical College of Japan

“The deadly wars in Ukraine, Syria, and Iraq have shown the continuing potential and real risks of large-scale use of banned chemical and biological agents and munitions, while other malign applications are evident from recent chemical

assassination attempts in Russia, Britain, and Malaysia. This new volume by Crowley and Dando sheds light on the dangerously neglected threats from toxin and bioregulator weapons and gives stark warning that current failure to regulate the rapidly advancing chemical and life sciences could allow development of new forms of such weapons capable of attacking diverse human life processes. It well argues for the need to urgently strengthen implementation of both the Biological and Toxin Weapons Convention and Chemical Weapons Convention to comprehensively address these dangers. It is highly recommended to all readers involved in international law and security; arms control, disarmament and non-proliferation; chemical and biological research and industry; and associated science and technology horizon scanning.”

—Paul F. Walker, *Vice Chair, Arms Control Association,
and International Coordinator, CWC Coalition*

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ABBREVIATIONS

AB2K	Afterburner 2000 System
AFOSR	Air Force Office of Scientific Research
APC	Antigen-presenting cell
ARDEC	Armament Research, Development and Engineering Center
ARL	Army Research Laboratory
ARPA	Advanced Research Projects Agency
BA	Biological Agent
BAA	Broad Agency Announcement
BBB	Blood-brain barrier
BDRP	Biological Defense Research Program
BMSU	Baqiyatallah University of Medical Sciences
BoNT	Botulinum Neurotoxin
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies
BTA	Biothreat Agent
BTWC	Biological and Toxin Weapons Convention
BW	Biological Warfare/Biological Weapon
BWA	Biological Warfare Agent
BWP	Biological Weapons Programme
CAD	Central Analytical Database
CAS	Chinese Academy of Sciences
CBDCOM	Chemical and Biological Defense Command
CBM	Confidence-Building Measure
CBMS-JVAP	Chemical Biological Medical Systems Joint Vaccine Acquisition Program
CBW	Chemical and Biological Weapons
CCK ₂	Cholecystokinin receptor
CCK-4	Cholecystokinin-4

CIA	Central Intelligence Agency
CNS	Central Nervous System
COIN	Counter-Insurgency Operations
COVID-19	Coronavirus disease caused by SARS-CoV-2 virus
CR	Dibenz[b,f][1,4]oxazepine
CRF	Corticotropin-Releasing Factor
CRISPR/Cas	Genome Editing Technology
CS	2-Chlorobenzylidenemalonitrile
CSP	Conference of States Parties
CTR	Cooperative Threat Reduction
CW	Chemical Warfare/Chemical Weapon
CWC	Chemical Weapons Convention
CWPF	Chemical Weapons Production Facility
CWS	Chemical Warfare Service
DARPA	Defense Advanced Research Projects Agency
DHS	Department of Homeland Security
DIBER	Defence Institute of Bio-Energy Research
DNA	Deoxyribonucleic Acid
DNI	Director of National Intelligence
DoD	Department of Defense
DRDO	Defence Research and Development Organisation
DRL	Defence Research Laboratory
DTC	Deseret Test Center
EC	Executive Council
ECBC	Edgewood Chemical Biological Center
ED	Effective Dose
ERDEC	Edgewood Research, Development and Engineering Center
EU	European Union
FAS	Federation of American Scientists
GABA	Gamma Amino Butyric Acid
GC-MS	Gas-Chromatography Mass Spectroscopy
GPC	General Purpose Criterion
GTX	Gonyautoxin
HIT	Hibernation Induction Trigger
IBB	Institute for Biochemistry and Biophysics
ICA	Incapacitating Chemical Agent
ICRC	International Committee of the Red Cross
IDF	Israel Defense Forces
IDFM	Indirect Fire Munition
IFC	Intermediate Force Capabilities
IHL	International Humanitarian Law
IHRL	International Human Rights Law
IHU	Imam Hossein University

IJCI	International Joint Cancer Institute
IL	Interleukin
IRGC	Iranian Republican Guard Corp
ISU	Implementation Support Unit
IUPAC	International Union of Pure and Applied Chemistry
JAG	Judge Advocate General
JNLWD	Joint Non-Lethal Weapons Directorate
JNLWP	Joint Non-Lethal Weapons Program
KGB	Committee for State Security
LC	Locus Coeruleus
LCt	Lethal Exposure Concentrations Relative to Time
LD	Lethal Dose
mAb	Monoclonal Antibody
MBP	Myelin Basic Protein
MCBW	Mass Casualty Biological (Toxin)Weapon
MHC	Major Histocompatibility Complex
MOOTW	Military Operations Other Than War
MOU	Memorandum of Understanding
MRICD	Medical Research Institute of Chemical Defense
MSP	Meeting of States Parties
MX	Meeting of Experts
NBACC	National Biodefense Analysis and Counter-Measures Center
NBTCC	National Biological Threat Characterization Center
NCF	Nonlethal Riot Control Combinational Formulation
NEER	Nonlethal Environmental Evaluation and Remediation (Center)
neoSTX	neo Saxitoxin
NGO	Non-Governmental Organization
NHPs	Non-Human Primates
NIH	National Institutes of Health
NLMM	Non-lethal Mortar Munition
NLW	Non-Lethal Weapon
NORINCO	China North Industries Corporation
NRCGEB	National Research Center of Genetic Engineering and Biotechnology
NSDM	National Security Decision Memorandum
NTI	Nuclear Threat Initiative
OC	Oleoresin Capsicum
OCPF	Other Chemical Production Facilities
OPCW	Organisation for the Prohibition of Chemical Weapons
PAVA	Pelargonic Acid Vanillylamide
PBA	Pharmaceutical Based Agent
PG	Staphylococcal Enterotoxin B Agent
PLA	People's Liberation Army

PRC	Peoples' Republic of China
PREPARE	Pre-emptive Expression of Protective Alleles and Response Elements
PRES	Posterior Reversible Encephalopathy Syndrome
PSP	Paralytic Shellfish Poisoning
PST	Paralytic Shellfish Toxin
PTSD	Post-Traumatic Stress Disorder
PTX	Palytoxin
P&T	Pathogens and Toxins
RCA	Riot Control Agent
RDEC	Research Development and Engineering Center
RF	Relevant Facilities
RNA	Ribonucleic Acid
R&D	Research and Development
SAB	Scientific Advisory Board
SBIR	Small Business Innovation Research (Program)
SCIF	Sensitive Compartmented Information Facility
SEB	Staphylococcal Enterotoxin B
SIPRI	Stockholm International Peace Research Institute
STX	Saxitoxin
S&T	Science and Technology
SWAT	Special Weapons and Tactics
T-2	Trichothecene Mycotoxin T-2
TCR	T-Cell Receptor
TSU	Tear Smoke Unit
TWG	Temporary Working Group
UAV	Unmanned Aerial Vehicle
UK	United Kingdom
UN	United Nations
UNIDIR	United Nations Institute of Disarmament Information and Research
UNODA	United Nations Office of Disarmament Affairs
UNOG	United Nations Organisation at Geneva
UNSGM	United Nations Secretary-General's Mechanism
US	United States
USFOR-A	US Force Afghanistan
UxS	Unmanned System
VKS	Variable Kinetic System
VX	Venomous Agent X (Nerve Agent)
WHO	World Health Organization
WMD	Weapon of Mass Destruction
ZKA	Customs Office of Criminal Investigations

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Introduction

1.1 THE PURPOSE AND STRUCTURE OF THE BOOK

The chemical, life, and associated sciences are undergoing a revolution in capabilities that is allowing scientists to understand and manipulate living systems in unprecedented ways. This shift in the power of these sciences was epitomised by Jennifer Douda, the Nobel Prize winner for her work on the CRISPR/Cas gene editing system, when she titled her book recounting the discovery and its rapid spread around the scientific world *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*.¹ Moreover, it is widely accepted amongst the scientific community that this process of advance, which must give us more and more ability to improve our health and agriculture systems will continue at its current high rate for decades and will range across the whole of the life and associated sciences.²

This book explores one area of this rapidly evolving scientific landscape, namely contemporary dual-use research and associated activities related to toxins and bioregulators. Although such research may have legitimate

¹Douda, J. A. and Sternberg, S. H. (2018) *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*. Penguin Books, London.

²For an example of this, see the paper by the Director of the US BRAIN Initiative explaining the transformation of neuroscience resulting from the \$5 billion funding of the initiative between 2014 and 2026: Ngal, J. (2022) BRAIN 2.0: Transforming neuroscience. *Cell*, **185**, <https://doi.org/10.1016/j.cell.2021.11.037>.

benign purposes, it could potentially be—rightly or wrongly—construed as being intended to facilitate weaponisation of such agents, or for other malign purposes, for use against human beings.³ The book incorporates a series of illustrative country case studies highlighting areas where concerns or misperceptions might arise and explores how States can ensure that such research and related activities are not utilised in State-run chemical and biological weapons (CBW) development programmes,⁴ or misinterpreted as being utilised for such purposes. This book is intended as a companion to an investigation by the same authors of dual-use research and associated activities concerning a variety of pharmaceutical toxic chemicals that could potentially be employed in the development of incapacitating chemical agent (ICA) weapons.⁵

Chapter 1 briefly outlines the scope of agents covered, the existing regulatory regime, the nature of dual-use research, and the methodology employed in this publication. Chapter 2 reviews current research and possible future trajectories of research on toxins and bioregulators that could raise dual-use concerns. Chapters 3, 4, 5, 6, 7, and 8 comprise six country case studies exploring dual-use research of potential concern in China, India, Iran, Russia, Syria, and the US. Chapter 9 reviews the application of the most relevant arms control and disarmament instruments (i.e. the Geneva Protocol, the Biological and Toxin Weapons Convention [BTWC], and the Chemical Weapons Convention [CWC]) and other relevant measures to dual-use toxin and bioregulator research. Then Chap. 10 discusses our findings and conclusions, and provides recommendations to address these issues.

³The potential application of the chemical and life sciences in development of toxin weapons for use against animals or plants is outside the scope of this book. See, for example: Whitby, S. The future of chemical weapons: advances in the development of anti-plant agents; and Millet, P. The future of chemical weapons: advances in anti-animal agents, both in: Crowley, M. et al. (eds) *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*, Royal Society of Chemistry, 2018.

⁴This publication focuses exclusively on the potential misapplication of dual-use bioregulator and toxin research in State weapons programmes. For analysis of the development and use of toxin weapons by terrorist organisations and other non-State actors see for example: Jefferson, C. (2015) Biological weapons as weapons of terror: perspectives on the threat. Chapter 4 in S. Whitby et al. (Eds.) *Preventing Biological Threats: What You Can Do*. University of Bradford, Bradford; Bokan, S., Breen, J. and Orehovec, Z. (2002) An Evaluation of Bioregulators as Terrorism and Warfare Agents. *ASA Newsletter*, 90, 1 and 16–19.

⁵See Crowley, M. and Dando, M. R. (2014) *Down the slippery slope? A study of contemporary dual-use chemical and life science research potentially applicable to incapacitating chemical agent weapons*. University of Bath and University of Bradford, October.

1.2 SCOPE OF AGENTS AND ACTIVITIES COVERED

1.2.1 *Toxins*

There is some ambiguity of the meaning of “toxins” and the range of substances covered by this term both in the medical-scientific literature and also the arms control and disarmament discourse. For example, although expressly covered under the scope of the Biological and Toxin Weapons Convention, toxins are not explicitly defined under that Convention. Certain pluri-lateral medical organisations have, however, sought to characterise toxins. According to the World Health Organization (WHO) Second Edition of *Public Health Response to Biological and Toxin Weapons*:

although there is no consensus on the term among scientists, international law regards a wide range of substances as ‘toxins.’ At one end of the range are the bacterial toxins, such as botulinum toxin and staphylococcal enterotoxin, both of which have in the past been stockpiled for weapons purposes. They are high-molecular-weight proteins that can at present be produced on a significant scale only by the methods of industrial microbiology. In the middle of the range are the snake poisons, insect venoms, plant alkaloids and a host of other such substances, some of which are becoming accessible to chemical synthesis and others, e.g., curare, batrachotoxin and ricin, have been used as weapons. At the other end of the range are small molecules such as potassium fluoroacetate (found in the plant *Dichphalatum cymosum*), which are typically synthesized by chemical processes when they are needed even though they are also produced by certain living organisms, thereby falling within the legal definition of ‘toxin’. Hydrogen cyanide is another such toxin. It occurs in some 400 varieties of plant, in certain animals, and is synthesized by at least one bacterium (*Bacillus pyocyaneus*).⁶

Furthermore, certain States have defined toxins in their national legislation or associated national measures. Of particular note is the US, which has defined toxins as:

the toxic material of plants, animals, micro-organisms, viruses, fungi, or infectious substances, or a recombinant molecule, whatever its origin or method of production, including—(A) any poisonous substance or biological product that may be engineered as a result of biotechnology produced

⁶World Health Organisation (2004) *Public Health Response to Biological and Chemical Weapons*. 2ND edition, WHO, Geneva. p. 215.

by a living organism; or (B) any poisonous isomer or biological product, homolog, or derivative of such a substance.⁷

Consequently, given its broad scope, we will employ the US definition of toxins as our initial informal indicative working description of substances of potential concern to our study. We recognise, however, that it has not been formally endorsed by relevant international bodies (i.e., the BTWC States Parties or the Organisation for the Prohibition of Chemical Weapons [OPCW]).

We acknowledge the wide and open nature of our working description, incorporating a heterogeneous grouping of disparate substances. It should be noted that our working description does not restrict the range of substances covered solely to those causing death but instead encompasses the broader category of toxic material of natural origin and their synthetic analogues or derivatives, that can cause death, permanent harm or temporary incapacitation. This has important implications for the range of potential weaponised substances that we believe should be covered by national and international regulations and prohibitions. Where appropriate, we will refer to specific sub-sets of this overarching category that merit specific consideration, notably bioregulators (which are discussed in the next section).

A wide range of toxins have long been a cause of serious concern as potential weapons. A decade ago, a series of papers⁸ in the US Army *Combating WMD Journal*, for example, listed amongst others, botulinum toxin, shiga toxin, abrin, saxitoxin, tetrodotoxin, conotoxins, staphylococcal enterotoxins, and T-2 toxin. These toxins have also caused continuing concern amongst the medical⁹ and scientific communities.¹⁰ The 2018 edition of the US Army textbook *Medical Aspects of Biological Warfare*¹¹ has chapters on: ‘Botulinum Toxin’, ‘*Clostridium perfringens* Epsilon Toxin’, ‘Ricin’, ‘Staphylococcal Enterotoxin B and Related Toxins’, ‘Toxins and Venoms’, and ‘Poisons and Marine Algal Toxins of Concern’.

⁷United States Code; *Title 18, Crimes and Criminal Procedure; Chapter 10, Biological Weapons; Section 178, Definitions*. As cited in WHO (2004) op. cit., pp. 214–215.

⁸Nordin, J.S. (2012–2013) Biotoxins Used As Warfare Agents. *Combating WMD Journal*, Part I Issue 8, pp.3–7, Part 2 Issue 9, pp. 28–35 and Part 3 Issue 10, pp. 11–16.

⁹Berger, T. et al. (2016) Toxins as biological weapons for terror-characteristics, challenges and medical counter measures: a mini-review. *Disaster and Mil Med*, 2:7. DOI 10.1186/s40696-016-0017-4.

¹⁰Janik, E. et al. (2019) Biological Toxins as Potential Tools for Bioterrorism. *Int. J. Mol. Sci.*, 20, 1181. DOI:10.3390/IJMS20051181.

¹¹Bozue, J. B. et al. (Eds.) (2018) *Medical Aspects of Biological Warfare*. Office of the Surgeon General, The Borden Institute, Health Readiness Center of Excellence, Fort Sam Houston, Texas. (Chapters 14, 15, 16, 17, 18, 19).

The earlier 1997 textbook *Medical Aspects of Chemical and Biological Warfare*¹² included a chapter ‘Defense Against Toxin Weapons’ that had a list of some 21 known toxins, with their estimated lethality and sources. The author noted:

The botulinum toxins are so very toxic that lethal aerosol MCBW [Mass Casualty Biological (Toxin)Weapon] weapons could be produced with quantities of toxin that are relatively easily obtainable with present technology. They cause death through paralysis of respiratory muscles without producing microscopic changes in the muscles.

And that:

Staphylococcal enterotoxins, when inhaled, cause fever, headache, diarrhea, nausea, vomiting, muscle aches, shortness of breath, and a nonproductive cough within 2 to 12 hours of exposure. They can kill, but only at much higher doses.... These toxins, too, would probably be delivered as respirable aerosols.

The 2008 textbook *Medical Aspects of Chemical Warfare*¹³ had a list of some 63 known toxins and their sources. Table 1.1 lists some of these toxins (and their sources) for which there is evidence of possible utility in weapons to be found in the open literature.

It is well established that bacterial-derived toxins are among the most potent of natural toxins, with other (notably plant and fungal derived) toxins also having high potency; consequently, toxins from these categories have been the focus of previous, notably Cold War State, toxin weapons research and development programmes. It should be recognised that although many of these State weapons programmes concentrated on the development of lethal toxin weapons, a number of States including the Soviet Union and the US specifically sought to develop ‘non-lethal’ or

¹²Franz, D. R. (1997) Defense Against Toxin Weapons. Chapter 30 in F. R. Sidell et al. (Eds.) *Medical Aspects of Chemical and Biological Warfare*. Office of the Surgeon General, The Borden Institute, Health Readiness Center of Excellence, Fort Sam Houston, Texas. p. 609.

¹³Williams, P. et al. (2008) Toxins: Established and Emergent Threats. Chapter 19 in S. D. Tuorinsky (Ed.) *Medical Aspects of Chemical Warfare*. Office of the Surgeon General, The Borden Institute, Health Readiness Center of Excellence, Fort Sam Houston, Texas.

Table 1.1 Selected toxins with potential weapons utility

<i>Toxin</i>	<i>Source</i>
Abrin	Jequirity beans <i>Abrus precatorius</i> (plant)
Aconite	Roots of monkshood <i>Aonitum napellus</i> (plant)
Aflatoxin	<i>Aspergillus</i> moulds (fungi)
Botulinum toxin type A-G	<i>Clostridium botulinum</i> (bacteria)
Cholera toxin	<i>Vibrio cholerae</i> (bacteria)
Conotoxins	Pacific cone snails <i>Conus</i> species (animal)
Epsilon toxin	<i>Clostridium perfringens</i> (bacteria)
Palytoxin	Soft coral <i>Palythoa toxica</i> (animal)
Ricin	Castor beans <i>Ricinis communis</i> (plant)
Saxitoxin ^a	Dioflagellate marine algae (plant)
Shiga toxin.	<i>Escherichia coli/Shingella dysenteriae</i> (bacteria)
Staphylococcus aureus alpha toxin	<i>Staphylococcus aureus</i> (bacteria)
Tetanus toxin	<i>Clostridium tetani</i> (bacteria)
Tetrodotoxin ^b	Puffer fish and some salamanders (animal)
Trichothecene mycotoxin (T-2)	Fusarium species (fungi)
Western diamondback rattlesnake venom	<i>Crotalus atrox</i> (Texan diamondback) (animal)

Modified from reference 13

^a Named after the butter clam (*Saxidomus*) upon which the algae live

^b Its name derives from the order (*Tetraodontiforms*) that includes porcupinefish and pufferfish, which carry the toxin. It has also been found in blue-ringed octopuses

‘less lethal’¹⁴ toxin weapons that were purportedly intended to reversibly incapacitate or otherwise affect individuals, small groups, or in some cases extremely large numbers of individuals.¹⁵ For example, during the 1960s, staphylococcal enterotoxin B (SEB) was extensively investigated as a “less lethal” toxin weapon in the US biological weapons programme. In one test conducted in 1968, dry-agent SEB was released from US Phantom

¹⁴ According to a report commissioned by the UN Office of the United Nations High Commissioner for Human Rights (OHCHR), less lethal weapons are “designed or intended for use on individuals or groups of individuals and which, in the course of expected or reasonably foreseen use, have a lower risk of causing death or serious injury than firearms.” See: OHCHR (2020) *Guidance on less lethal weapons in law enforcement*.p. 45. Such weapons have sometimes been called non-lethal, although this term is becoming obsolete in recognition that the use of any weapon can have fatal consequences. Acknowledging the continuing contested discourse over the nature, scope and application of the terms non-lethal and less lethal weapon, the term “less lethal” will be placed in quotation marks when used by the authors during this publication.

¹⁵ For further discussion see in particular see Sect. 6.8 of the Russian case study and Sect. 8.2 of the US case study.

strike aircraft flying over caged monkeys and other animals at sea off Eniwetok Atoll in the Marshall Islands. The test data reportedly indicated a 30% casualty rate over an area of 2400 km².¹⁶

In recent years, the range of possible candidate toxin agents has grown markedly due to the potential malign application of contemporary advances in life sciences to facilitate, for example, the conjugation of different toxins (to deliver them to specific targets) or even the bespoke design of novel toxins (for research and medical applications). Consequently, this huge diversity of potential toxin agents has to be kept in mind when exploring the range of contemporary applicable chemical and life science research projects of potential concern. One area demanding particular attention is dual-use research relating to bioregulators.

1.2.2 *Bioregulators*

Bioregulators are naturally occurring chemicals produced within living organisms that help to ensure the proper functioning of vital physiological systems in those same living organisms. In mammals bioregulators are involved in the regulation of such core but diverse body functions as respiration, blood pressure, heart rate, body temperature, consciousness, mood, and the immune response. Advances in drug delivery have made bioregulators and the chemical analogues derived from them more attractive as potential medicines. Indeed, the growing understanding of these compounds and their role in the human body is likely to bring about profound changes in medicine through increasing the ability to intervene selectively in fundamental biological processes.¹⁷

In terms of chemical structure, bioregulators are extremely diverse, ranging from relatively simple molecules in the case of certain hormones or neurotransmitters to complex macromolecules such as proteins, polypeptides, or nucleic acids (here the descriptions ‘simple’ and ‘complex’ refer to their chemical structures). Their physiological action is not limited to any single mechanism, regulatory system, or organ. The same

¹⁶Perry Robinson, J. (2008) Bringing the CBW Conventions Together. *The CBW Conventions Bulletin*, **80**, 1–4. p. 3; Regis, E. (1999) *The Biology of Doom: The History of America’s Secret Germ Warfare Project*. Henry Holt, New York, pp. 201–204.

¹⁷For an extended discussion of these points see Trapp, R. (2012) Synthesis of Peptide Bioregulators, Chapter 11 in J. B. Tucker (Ed.) *Innovation, Dual Use, and Security: Managing the risks of emerging biological and chemical technologies*. James Martin Centre for Nonproliferation Studies, Monterey Institute of International Studies.

bioregulators can operate in and have different physiological roles in various tissues. Additional complexity arises because the nervous, endocrine, and immune systems interact. Consequently, altering the concentration of a bioregulator or interfering with its receptors in one system can affect the function of the other systems.

Research has provided insights into the role of bioregulator receptors in generating diverse physiological responses and has suggested how they might be manipulated. Trapp has stated that “because bioregulators maintain equilibrium in body systems, it should be possible, at least in principle, to design molecular analogues that affect body temperature, sleep, and even consciousness in a selective manner.”¹⁸

Many bioregulators are peptides, comprising short chains of amino acids. These can be artificially altered or synthesised, with even minor chemical modifications of such peptide bioregulators creating analogues with markedly different physiological properties. Similarly, the duration of a bioregulator’s action upon specific processes can be artificially extended by means of bespoke structural modifications that will slow its rate of degradation in the body, or by co-administration with another drug that suppresses or blocks the biological pathways responsible for its degradation.¹⁹ Understanding of the nature, mechanisms of action, and roles of bioregulators has grown at an astonishing pace in recent years. This has been stimulated and facilitated by new investigatory techniques and also the interaction of previously separate scientific disciplines. Trapp,²⁰ Dando,²¹ and Rose²² have all highlighted contemporary investigation of the functional chemistry of the brain as one of the fastest-growing areas of research in the life sciences. A significant part of this progress has been driven by the rapid increase in knowledge about neuropeptides and their receptor and sub-type receptor systems, an area that will only expand in future.

Advances in the understanding and use of peptide bioregulators have gone hand-in-hand with developments in peptide synthesis. Today commercial companies manufacture peptides to order in quantities ranging

¹⁸Trapp, R. (2012) op. cit. p. 174

¹⁹Koch, B. L. et al. (1999) Inhalation of Substance P and thiorphan: acute toxicity and effects on respiration in conscious guinea pigs. *J. Appl. Toxicol.*, **19**, pp. 19–23.

²⁰Trapp, R. (2012) op. cit. p. 174.

²¹Dando, M. R. (2020) *Neuroscience and the Problem of Dual Use: Neuroethics in the New Brain Research Projects*. Springer Nature, Cham, Switzerland.

²²Rose, S. (2009) *Prospects and Perils of the New Brain Science: A Twenty Year Time Scale*, Royal Society Neuropolicy Lab, Royal Society, London.

from milligrams for laboratory use to hundreds of kilograms for industrial applications. The choice of production method depends largely on the size of the peptide, its amino acid sequence, and the presence of modifications or protective groups. Overall, the chemical synthesis of peptides remains the most common method for industrial-scale production. In the future it may also be possible to produce large quantities of peptides in recombinant microorganisms or transgenic plants and animals.

Toxins, although very dangerous, have been honed by evolutionary processes of offence and defence to have very precise targets for their actions which has therefore proved to be very useful for scientific investigations and medical developments. However, because they have been honed by long evolutionary processes, they are not likely to be easily modified to make them much more specific. Bioregulators may have been less subject to such evolutionary forces and are therefore more likely to be modifiable to make them more precise and effective through the development of synthetic analogues.

The potential threats of the weaponisation of bioregulators and their use to manipulate specific physiological systems have been highlighted by certain States and academics. In its preparatory paper for the Sixth BTWC Review Conference analysing relevant scientific and technological advances, the Netherlands noted that excessive doses of bioregulators can cause severe physiological imbalances, including “heart rhythm disturbances, organ failure, paralysis coma and death, giving them a potential for misuse”.²³ Whilst Trapp has warned that bioregulators could be developed into “biochemical weapons that incapacitate, alter moods, trigger psychological imbalances, cause a variety of other types of physiological reactions, or kill.”²⁴

Bokan and Orehovec have highlighted certain characteristics of bioregulators that may encourage State interest in their weaponisation:²⁵

Some of these compounds may be potent enough to be many hundreds of times more effective than traditional chemical warfare agents. Some very important characteristics of new bioregulators that would offer significant

²³The Netherlands (2010) *Scientific and Technological Developments Relevant to the Biological Weapons Convention*, 6th BWC Review Conference, as cited in Trapp, R. (2012) op. cit. p. 173.

²⁴Trapp, R. (2012) op. cit. p. 176

²⁵Bokan, S. and Orehovec, Z. (2003) An Evaluation of Bioregulators/Modulators as Terrorism and Warfare Agents. Croatian Military Academy Report, 1 July 2003; See also Bokan, S, Breen, J. and Orehovec, Z (2002) An Evaluation of Bioregulators as Terrorism and Warfare Agents, *ASA Newsletter*, 90, 1 and 16–19.

military advantages are novel sites of toxic action; rapid and specific effects; penetration of protective filters and equipment and militarily effective physical incapacitation.

However, that may be an unlikely projection, given the chemical and physical constraints that apply to bioregulators, which are no different to those of other toxic chemicals, against which modern protective equipment is efficient.

Once again it is important to note that previous State biological weapon programmes—including those of the Soviet Union and the US—explored the development of both lethal and “less lethal” bioregulator-based weapons.²⁶ For example, from the late 1970s onwards, the Soviet Union undertook clandestine bioregulator weapons research and development including through Project Bonfire which sought to develop bioregulator weapons that, according to one former Soviet whistleblower, “could damage the nervous system, alter moods, trigger psychological changes, and even kill”.²⁷

As more and more has become known about the nature and action of specific bioregulators and the biological systems they affect, a growing number have been identified in the open academic and State scientific literature as being of potential dual-use concern. For example, a Canadian study sent to all States Parties for the 1991 Third Review Conference of the BTWC had sections discussing 13 different bioregulators.²⁸ Subsequently, a 2003 study by Bokan and Orehovec and a 2005 review by Madsen, both set out bioregulator categories and gave illustrative examples of the different types.²⁹ Again, some examples of bioregulators where there is evidence of concern about potential misuse in the open literature are listed in Table 1.2.

The effects of these bioregulators on behaviour can be startlingly specific. For example, one recent review concluded that:³⁰

²⁶For further discussion in particular see Sect. 6.8 of the Russian case study and Sect. 8.2 of the US case study.

²⁷Alibek, K. and Handelman, S. (1999) *Biobazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World—Told from the Inside by the Man Who Ran It*. Random House, New York, p. 164.

²⁸Dando, M. R. (2006) *The New Biological Weapons: Threat, Proliferation and Control*. Lynne Rienner, Boulder, Colorado. See Chapter 5 Bioregulatory Peptides, pp. 67–86.

²⁹Bokan, S. and Orehovec, Z. (2003) op.cit.; Madsen, J. M. (2005) Bio Warfare and Terrorism: Toxins and Other Mid-Spectrum Agents, pp. 273–279 in P. Wexler (Ed.) *Encyclopedia of Toxicology*, Academic Press, New York.

³⁰Rehfeld, J. F. (2021) Cholecystokinin and Panic Disorder: Reflections on the History and Some Unsolved Questions. *Molecules*, 26, 5657. <https://doi.org/10.3390/molecules26185657>, p. 3.

Table 1.2 Selected bioregulators with potential weapons utility

<i>Bioregulator category</i>	<i>Relevant effects</i>
<i>Cytokines</i>	
Interleukin 1 and Interleukin 6	Increase body temperature (fever)
<i>Neurotransmitters and hormones</i>	
Opioids (endorphins and enkephalins)	Sedation (and death at high doses)
Substance P	Prevents normal breathing
Cholecystokinin	Causes panic attacks
Endothelins	Increase blood pressure
Oxytocin	Controls aspects of human behaviour including trust
<i>Vasoactive plasma proteases</i>	
Bradykinins	Reduce blood pressure

Modified from references 28 and 29

Today, nobody questions CCK-4 [Cholecystokinin-4] as a robust panicogenic peptide, that is and has been a reliable tool in the study of panic disorder in man, and anxiety in most mammals. It is also well-established that CCK-4, of course, targets the cerebral CCK₂-receptor and interacts in the provocation of anxiety with other neurotransmitter systems.

And as with toxins, it is to be expected that there will be a great deal more discovered as research on these bioregulators continues.

1.2.3 *Other Chemicals of Biological Origin*

There is currently no consensus amongst the international arms control and scientific communities regarding the formal definition of toxins nor the full scope of chemicals that should be considered as toxins. This, in turn, appears to have contributed to some uncertainty and divergent interpretation amongst States regarding the regulation of toxins under relevant arms control and disarmament instruments, notably the BTWC and CWC. This may also have affected whether, and if so how, States address a broad and overlapping range of substances of biological origin (and their synthesised analogues) that have been, or may in the future be, weaponised. It elicits open questions as to whether at least, some of these substances should be considered to be toxins and regulated accordingly. And for those not considered to be toxins it raises questions as to how they should be classified and regulated.