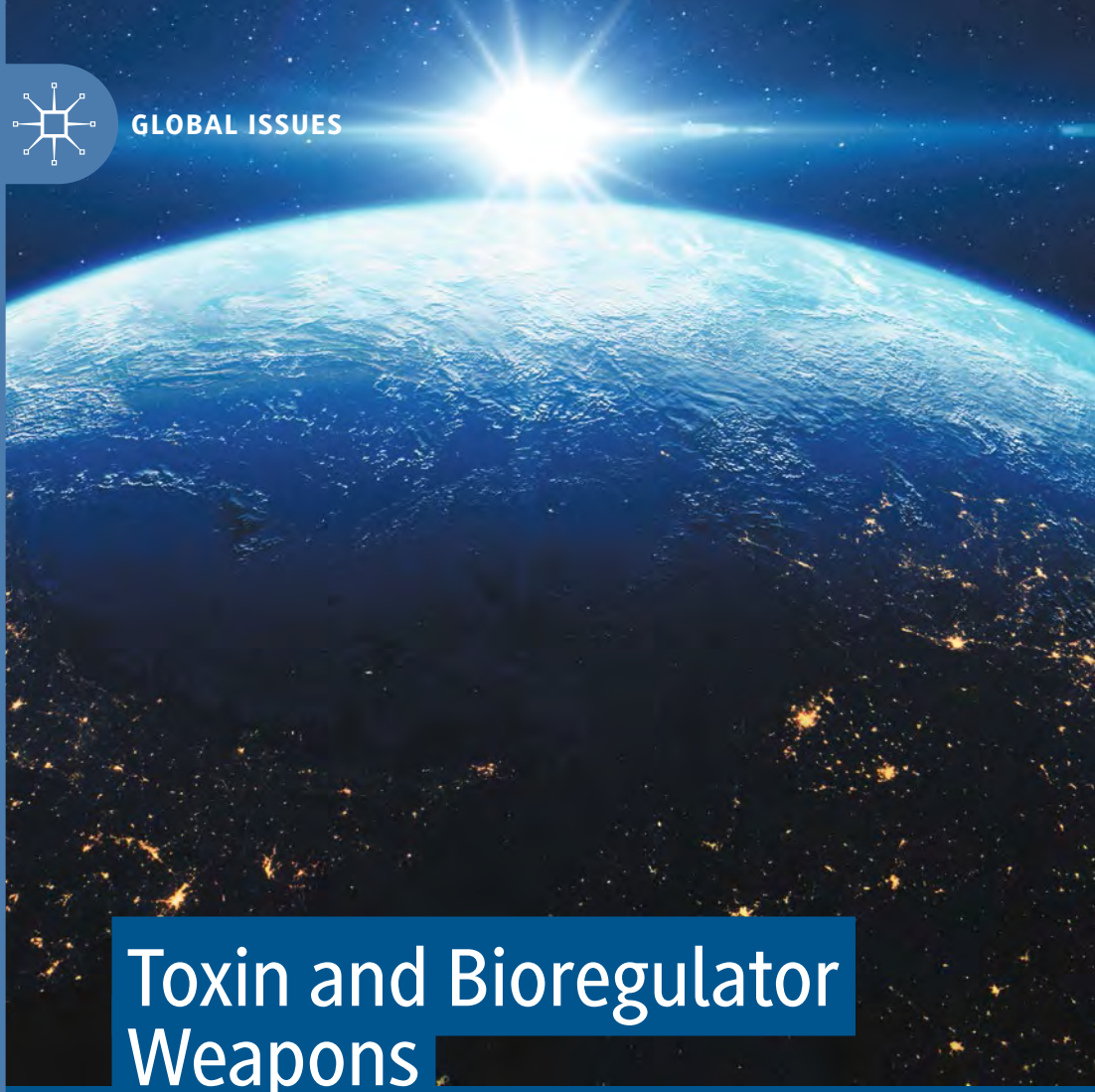

GLOBAL ISSUES

Toxin and Bioregulator Weapons

Preventing the Misuse of the Chemical and Life Sciences

Michael Crowley
Malcolm R. Dando

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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.

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

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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 bio-regulators 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*

Contents

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	Cholecytokinin receptor
CCK-4	Cholecytokinin-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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CHAPTER 1

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

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

[2] For 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.cell2021.11.037.

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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.

[3] The 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.

[4] This 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.

[5] See 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

[6] World 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 heterogenous 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 papers[8] 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 medical[9] 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'.

[7] United 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.

[8] Nordin, 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.

[9] Berger, 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.

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

[11] Bozue, 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 Huston, 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

[12] Franz, 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 Huston, Texas. p. 609.

[13] Williams, 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 Huston, Texas.

Table 1.1 Selected toxins with potential weapons utility

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

[16] Perry 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.

[17] For 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 Rose[22] 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

[18] Trapp, R. (2012) op. cit. p. 174

[19] Koch, 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.

[20] Trapp, R. (2012) op. cit. p. 174.

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

[22] Rose, 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

[23] The 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.

[24] Trapp, R. (2012) op. cit. p. 176

[25] Bokan, 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]

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

[27] Alibek, K. and Handelman, S. (1999) *Biohazard: 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.

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

[29] Bokan, 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.

[30] Rehfeld, 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

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

Modified from references 28 and 29

> Today, nobody questions CCK-4 [Cholecytokinin-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 CCK_2-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.

These considerations are particularly pertinent when addressing research, associated development and use of those "less lethal" weapons employing substances of biological origin (and their synthesised analogues). This publication consequently explores the contested discourse with regards to three "less lethal" weapon categories that include such substances:

- Riot control agents (RCAs) are chemicals which rapidly produce sensory irritation or disabling physical effects which disappear within a short time following termination of exposure. RCAs employed in large amounts or in enclosed spaces can cause serious, sometimes fatal, health effects. RCAs commonly employed in law enforcement include a number of substances of biological origin notably the capsaicinoids and a further chemically synthesised analogue, pelargonic acid vanillylamide (PAVA).
- Malodorants are a disparate group of naturally occurring and synthesised chemicals affecting the human olfactory receptors, employed to elicit short-term and temporary physiological effects or behavioural responses.
- Incapacitating chemical agents (ICAs) (also called central nervous system (CNS) acting chemical agents) are a disparate group of chemicals whose purported intended purpose is to cause prolonged but non-permanent disability or incapacitation; they include centrally acting agents producing loss of consciousness, sedation, hallucination, incoherence, paralysis, disorientation, or other such effects. Many putative ICAs have low safety margins. Inappropriate doses cause serious, sometimes permanent, health effects and may result in death. Chemicals of biological origin and their synthetic analogues have been amongst the substances explored as potential incapacitating chemical agents.

1.3 Coverage of Toxins and Bioregulators Under International Arms Control and Disarmament Instruments

The norm against the deliberate use of both poison and disease as weapons of warfare can be traced back to antiquity. These ancient interconnected taboos subsequently became embodied, codified, and expanded in the twentieth century and continue to this day through three international

instruments: the Geneva Protocol, the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC). Collectively they establish two distinct yet overlapping regimes prohibiting chemical and biological weapons which, in theory at least, both cover toxins and bioregulators.

Adopted in 1925, the Geneva Protocol prohibits the use in war of biological and chemical weapons, including toxins and bioregulators. This normative prohibition, which subsequently became established as customary international law applicable to all States, was the essential bedrock upon which the more comprehensive prohibitions established under the BTWC and CWC could be built. However, because its prohibitions relate solely to use, the Geneva Protocol has no direct utility in regulating dual-use research and associated development of toxin and bioregulator weapons.

The BTWC, which was adopted in 1972, contains no explicit definition of toxins. However toxins—both natural toxins and bioregulators and their analogues—are captured in the BTWC's Article I which states that:

> Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain [inter alia]:
>
> 1. Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes…

This breadth of coverage—which does not discriminate on grounds of lethality—has been repeatedly confirmed and applied to advancing science and technology in Additional Understandings incorporated into successive *Final Documents* of BTWC Review Conferences (as explored further in Chap. 9).

The 2004 World Health Organization Second Edition of *Public Health Response to Biological and Toxin Weapons* explains the nature and scope of such coverage and its implications for bioregulators:[31]

> In the sense of the Biological and Toxin Weapons Convention, 'toxin' includes substances to which scientists would not normally apply the term. For example, there are chemicals that occur naturally in the human body that would have toxic effects if administered in large enough quantity. Where a scientist might see a bioregulator, say, the treaty would see a poisonous substance produced by a living organism, in other words a toxin.

[31] World Health Organisation (2004) *Public Health Response to Biological and Chemical Weapons.* 2ND edition, WHO, Geneva. p. 216.

And the text continued:

> nor is this unreasonable. Wasp venom, for example, is clearly a toxin, yet its active principle is histamine, which is also a human bioregulator. Although histamine might not itself be made into an effective weapon, the same cannot necessarily be said for other bioregulators.

Similarly, toxins and bioregulators—again regardless of the lethality of their effects—are also covered under the scope of the 1993 Chemical Weapons Convention. Article I of this Convention prohibits the development, production, stockpiling, transfer or use of 'Chemical Weapons', which are defined under Article II:

> 1. 'Chemical Weapons' means [inter alia]:
>
> a. Toxic chemicals and their precursors, except where intended for purposes not prohibited under the Convention, as long as the types and quantities are consistent with such purposes.

And

> 2. 'Toxic Chemical' means:
>
> Any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, in munitions or elsewhere.

In their revised *Commentary on the Chemical Weapons Convention*, Krutzsch and Trapp have highlighted the importance of the coverage of toxins under both the BTWC and the CWC:

> This overlap recognizes that it is impossible to draw a line between toxins and other toxic chemicals: an increasing number of toxins can be synthesized in laboratories without resorting to organisms which produce them in nature, and a number of low-molecule-weight toxins are at the same time synthetic chemicals manufactured by industry (e.g., hydrogen cyanide). At the same time, biotechnological manufacturing methods have increasingly come into use for chemicals which were traditionally produced via chemical synthesis only.[32]

[32] Krutzsch, W. and Trapp, R. (2014) Article II: Definitions and Criteria, in Krutzsch, W., Myjer, E. and Trapp, R. (Eds.) *The Chemical Weapons Convention: A Commentary*. Oxford, Oxford University Press. p. 85.

However, as will be explored in Chap. 9, in reality, this overlap of BTWC and CWC regime scope masks a potential regulatory gap in the application of both Conventions, with neither treaty being effectively implemented by the States Parties so as to ensure that toxins and bioregulators are not developed as weapons.

As Julian Perry Robinson warned:

> Such overlap ought to mean, one might think, that the weapons [including toxins, bioregulators and other bioactive chemicals of biological origin, as well as their synthetic analogues] are well controlled, being subject not just to one but to two international disarmament treaties. In the real world, however, that is not the way it is. That overlap seems simply to have given people involved in implementing one of the two treaties opportunity to relinquish, even deny, responsibility for anything also covered by the other treaty. The area of overlap thus risks becoming a gulf into which things disappear. It looks like this has been happening to toxins.[33]

Given that Perry Robinson raised these concerns in 2008, a central focus of this publication is to investigate whether and how the situation today has altered after over a decade of very rapid advances in the life and associated sciences.

1.4 Dual-Use Research and the Difficulties with Establishing Intent

Dual-use is a concept that can be applied to the tangible and intangible features of materials or technology that enable utilisation for both hostile and peaceful ends with no, or only minor, modifications.[34] Authors who have examined historical attempts by a State to utilise dual-use materials and technologies in a biological weapons programme have highlighted the importance of *intent* in determining whether a particular dual-use technology or agent is so employed. The hostile use of a specific agent or

[33] Perry Robinson, J. (2008) Op.cit. p. 2.

[34] Molas-Gallart, J. and Perry Robinson, J. (1997) *Assessment of Dual-use Technologies in the Context of European Security and Defence*. Report for the Scientific and Technological Options Assessment (STOA), European Parliament. As cited in McLeish, C. and Nightingale, P. (2007) Biosecurity, bioterrorism and the governance of science: The increasing convergence of science and security policy. *Research Policy*, **36**, 1635–1654. p. 1636.

technology does not arise *automatically* from the inherent properties of that agent or technology but requires the *active intervention* of relevant actors.[35] Although these concepts can be employed in a variety of contexts and for a variety of materials and technologies, they are, of course, central to the understanding of the concerns explored in this publication.

Dando, Pearson, Rozsa, Robinson, and Wheelis have previously noted that[36]:

> A fundamental characteristic of BW [Biological Weapons] is the dual-use nature of both the agents and the equipment needed to produce the agents. As biological agents (microbes and toxins) occur in nature, the presence or absence of a particular agent or toxin cannot by itself be regarded as evidence of a prohibited activity. Nor does the presence or absence of equipment to produce the agent by itself indicate the presence or absence of a prohibited activity…. Underlying intention remains the determining consideration.

However, the authors further warned that "it is difficult to be certain whether a program on which information becomes available is a national offensive program or merely an ongoing program for permitted purposes—prophylactic, or other peaceful purposes."

The importance of determining the intent behind a specific toxin or bioregulator dual-use research programme is heightened given how such research is covered by both the BTWC and CWC. Whilst the Conventions prohibit the development and production of biological or chemical (and therefore toxin and bioregulator) weapons, neither Convention prohibits research into such substances *per se*, even if such dual-use research could potentially be used for weaponisation purposes. Such research would only be prohibited if it were actually part of a weaponisation process. In fact, as explored in Chap. 9, both Conventions expressly permit the conduct of research and associated activities, including the production of appropriate quantities of potential weapons agents for "prophylactic, protection and

[35] McLeish, C. and Balmer, B. (2012) Development of the V-Series Nerve Agents, pp. 273–287 in: J. 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. July.

[36] Wheelis, M., Rozsa, L and Dando, M. R. (Eds.) (2006) *Deadly Cultures: Biological Weapons Since 1945*. Harvard University Press, Harvard. (Chapter 17 Analysis and Implications, pp. 361–362).

other purposes" under the BTWC and "protective purposes" under the CWC.

In the current situation of very rapid advances in military-and-security-relevant dual-use life science, States will need to closely monitor developments and, if necessary, establish appropriate protective measures to ensure that they are not vulnerable to attack. Yet, in attempting to stay at the forefront of relevant fields of research, the so-called Security Dilemma can come into play, with States reacting and counter-reacting to reported research and related activities in other States in such a way as to inadvertently make the situation more dangerous for everyone. US Ambassador (Ret.) Donald A. Mahley, in an interesting reflection on his experience a decade earlier in the BTWC Protocol negotiations, pointed out the difficulty of inspection in such situations:[37]

> While the US was not pursuing offensive BW [biological weapons] capability, we were (and still are) pursuing both defense against potential BW acts whether by rogue nations or by terrorists, and, separately, against exotic diseases in various parts of the world that might pose threats to US service members. Depending on the attitudes of inspectors, it would be equally difficult to *prove the negative* about the capabilities inherent in either of these legitimate investigations. (Original emphasis)

Clearly, the international context and the history of the relationships between the States involved in making such judgements will have consequences for how such judgements are made. We have sought to acknowledge and highlight such realities in our illustrative country case studies.

An analysis of dual-use research will comprise two inter-related aspects, firstly determining and reviewing the relevant types of research and associated activities of potential concern; and secondly seeking to establish and apply relevant indicators of intent potentially driving such activities. In this publication we have attempted to utilise illustrative country case studies to explore how effectively the international system as a whole is managing these difficult and entangled issues; and to highlight the inherent dangers and potential consequences of its failure to identify (or conversely, wrongly identify) research and associated activities as being part of a State's weapons programme.

[37] Ambassador Mahley, D. A. (2010) A Personal Assessment of the BWC Protocol Negotiations. *The CBW Conventions Bulletin*, **86**, 1–5. p. 3.

The search for candidate toxins and bioregulators with potential weapons utility—and consequently, the range of research and associated activities of potential dual-use concern—is likely to be informed by current advances in pharmacology, genomics, and related disciplines which have revolutionised our understanding of the body's bioregulatory systems and notably brain neurotransmitter/neuroreceptor systems. Although such research is at a relatively early stage in the understanding of the ways in which biologically active peptides and related chemicals are employed in the body's regulatory systems and the brain's information-processing system, the search for novel toxins and bioregulator weapons may prove attractive to certain States as new potential opportunities arise.

In such circumstances, in addition to work on efficient new methods of extraction and production of known toxins and bioregulators (including by chemical synthesis), other dual-use research could also raise concern. For example, attempts to modify existing toxins and bioregulators, or design and synthesise novel (more effective) analogues of known agents, to study the structure of known receptor sub-types and their interaction with relevant toxins and bioregulators, to explore and modify bioregulatory systems, or to explore novel packaging and transportation of peptides to potential targets within the body might raise legitimate concerns or be misperceived if there was not adequate transparency to ensure that peaceful intentions were well understood. Similarly, studies exploring potential toxin, bioregulator or surrogate agent aerosolisation, dispersal, and uptake for which there appears to be little justification for medical, veterinary, or other peaceful purposes need to be closely reviewed and evaluated. In addition to monitoring such processes, it is important to look beyond research directly connected to particular potential candidate toxin and bioregulators or means of delivery, and also explore the mechanisms by which such research may be transformed from that undertaken to further knowledge, or for the development of drugs or other measures to alleviate illness and disability, to be instead employed in the development of weapons. Such considerations have informed the indicators of potential concern utilised in the open-source survey conducted by the authors, as discussed next.

The process of definitively determining the intent behind relevant State research programmes and associated activities of potential concern will be extremely difficult and highly contested, and is certainly beyond the capabilities and capacities of the current authors. It will be complicated by the need to explore and attempt to understand the motivations of the specific

actors involved, notably the military, security, law enforcement, and other State structures under which such research is undertaken, funded, or authorised. This should, in turn, be informed by an investigation and analysis of historical and contemporary factors potentially influencing relevant State activity including the political, human security and national security environment of that country; and specifically, any security and military doctrine and threat perceptions related to chemical and biological weapons.

The difficult and contested process of determining the intent behind specific dual-use research and associated activities of potential concern is further complicated by the employment of threat (or risk) assessments by certain States as part of their biological or chemical defence programmes. Such threat assessment can involve the development (normally in limited amounts) and study of biological or chemical weapons agents and relevant means of delivery in order to assess existing defensive vulnerabilities of that State and guide the development of effective counter-measures by that State. This approach is highly problematic, firstly, because such activities could be readily used as a cover for the development and subsequent large-scale production of biological or chemical weapons. Secondly, even when the intention behind such activities is completely benign, such threat assessments could, depending on the specific activities, as well as the agents and means of delivery concerned, directly breach the ban on weapons development enshrined in the BTWC[38] or CWC,[39] or in the case of toxins and bioregulators, both Conventions. Here the level of transparency of the State Party is critical to determining whether this might be the case. These issues will be raised in certain country case studies and will be further discussed in Chap. 9 of this book.

The difficulties of determining intent are further complicated by an overlapping secondary conception of dual-use, namely a technology that can have either a military or civilian (including law enforcement) function. Both this and the main definition of dual-use employed in this book may well intersect and need to be read together, notably with regard to considerations of the legitimacy under the CWC and BTWC of the research,

[38] Tucker, J. B. (2008) The body's own bioweapons. *Bulletin of the Atomic Scientists*, **64**(1), pp. 16–22 and pp. 56–57.

[39] See: Krutzsch, W. and Trapp, R. (2014) Article II: Definitions and Criteria, in Krutzsch, W., Myjer, E. and Trapp, R. (eds) *The Chemical Weapons Convention: A Commentary*, Oxford, Oxford University Press. p. 85.

development and use of certain toxins and bioregulators (and associated technologies) purportedly intended for law enforcement purposes. These considerations are particularly pertinent when considering potential dual-use research and associated development of "less lethal" law enforcement weapons employing substances of biological origin, notably riot control agents, malodorants, and incapacitating chemical agents. Once again these issues will be raised in certain country case studies and will be further examined in Chap. 9.

It has to be stressed finally that research on toxins and bioregulators is of considerable medical interest at the present time and that such benignly intended activities will rightly continue to be heavily funded and will deliver novel and important results. Moreover, the civil scientists involved in this benignly intended work are unlikely to have much knowledge of the dual-use implications of their work.

1.5 Methodology

In general terms, we follow a Holistic Arms Control methodology. This consists of a three-stage process where consideration is given first to analysis of the weapons and technologies of concern; then to the full range of directly applicable arms control and disarmament instruments, relevant international law, and other potential regulatory measures; and finally a bespoke strategy developed to strengthen existing measures and/or develop new measures to address the existing weapon systems and technologies and respond to likely future developments.[40] The research reported here employs this integrated process.

For this project a survey of open-source literature on dual-use toxin and bioregulator research of potential concern was carried out in two stages. In stage 1 a survey was undertaken including of: government documents and academic studies pertaining to past State toxin or bioregulator weapons related activities; scientific and medical databases and publications detailing contemporary research activities in relevant disciplines; and research and technology monitoring and evaluation reports from bodies

[40] For further discussion of Holistic Arms Control and its application see: Crowley, M. (2016) Chemical Control: *Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery.* Palgrave Macmillan, Basingstoke. See pp. 4–7 for definition and then application throughout the publication; see also: Crowley, M. et al. (eds) (2018) *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*, Royal Society of Chemistry, London.

such as the BTWC Implementation Support Unit (ISU), Scientific Advisory Board of the OPCW, the US State Department, UK Royal Society, the International Union of Pure and Applied Chemistry (IUPAC), Spiez Laboratory, and Penn State University. The information obtained was then reviewed against a range of indicators of potential concern (detailed in Table 1.3), so as to narrow the focus of subsequent in-depth research conducted in stage 2 to a discrete number of illustrative country case studies (set out in Chaps. 3, 4, 5, 6, 7, and 8).

It must be emphasised that in our choice of the six countries subject for more in-depth analysis, we have attempted to explore a diverse range of differing scenarios and contexts under which dual-use research is undertaken and regulated. We have also attempted to incorporate some geographical spread, with countries chosen from the Americas, Asia, Europe, and the Middle East. Consequently, it needs to be emphasised that the countries are not chosen because they are considered the most meriting concern, and many other countries could have been selected in their stead. It is also important to acknowledge that our country choices were in part conditioned and limited by other factors such as the availability of sufficient open-source material, particularly in English. Consequently, the country studies are intended to be illustrative of the difficulties of management of the problem of dual-use that face all members of the international community.

Information concerning activities potentially related to toxin and bioregulator weapons research and development has proven difficult to uncover and substantiate; public access to such information is presumed to be severely restricted on stated national security grounds. Furthermore, the amount and quality of open-source information available for each country will vary, and in part be dependent upon the mechanisms established by that State to ensure oversight and accountability of relevant research and development activities, particularly those conducted or funded by military, security or law enforcement bodies, and the degree to which such measures facilitate reporting and transparency to the legislature and the public. Consequently, this review is by no means exhaustive, and the spread of State and civilian research entities cited in the country case studies does not purport to be a complete picture of contemporary research activities in this area. Instead, it reflects the open-source information (predominately in English) that could be obtained by the authors at the time.

For the country case studies, we have generally concentrated upon examining the nature of the relevant dual-use research and associated

Table 1.3 Factors that may indicate research and development activities of potential concern

A. *Information related to policy and practice associated with weaponisation of toxins and bioregulators*
   (a) Reported research, development, production, acquisition, stockpiling, deployment or use of toxin or bioregulator weapons by a State actor either inside its own territory or in the territory of another State that occurred prior to the coming into force of the BTWC and/or CWC
   (b) Reported development, production, acquisition, stockpiling and/or deployment of toxin or bioregulatory weapons by State actors, following the coming into force of the BTWC and CWC
   (c) Reported research activities conducted as part of State programmes that may or may not have succeeded in developing toxin or bioregulator weapons
   (d) Statements or publications by State entities advocating use of toxin and bioregulator weapons, intention to develop such weapons or solicitations for researchers to tender for such activities
   (e) Statements or publications by State entities indicating a lack of a clear understanding of relevant prohibitions embodied in the CWC and BTWC.

B. *Information on research establishments and personnel*
   Dual-use work (research and development) undertaken:
   (a) Under the auspices of research establishments controlled, directly or indirectly, by defence, security, or law enforcement organisations, or that receive significant funding from such organisations
   (b) Under the auspices of research establishments that have previously been engaged in toxin or bioregulator weapons research or development, or in the weaponisation of other biological or chemical agents
   (c) By scientists who have stated that they are conducting or have conducted research related to toxin or bioregulator weapons
   (d) By scientists with current or previous links to defence, security or law enforcement organisations and related research establishments
   (e) By scientists conducting research that could readily be employed in the development of toxins and bioregulators and/or associated means of delivery, and which has little or no direct and immediate relevance to medical, veterinary, or other peaceful purposes.

C. *Information on research on toxins and bioregulators*
   Dual-use research and/or development undertaken involving:
   (a) Studies of toxins and bioregulators that have previously been weaponised, including studies of their interaction with existing and new target physiological systems
   (b) Studies of the structure and function of receptors and their interaction with potential candidate toxin and bioregulator weapons
   (c) The discovery and characterisation of novel toxins and bioregulators with potential weapons utility
   (d) The modification of existing toxins and bioregulators or synthesis of novel toxins and bioregulators with potential weapons utility

(*continued*)

Table 1.3 (continued)

(e) Production of toxins and bioregulators with potential weapons utility
(f) Aerosolisation and other methods of dissemination and delivery of toxins, bioregulators or their surrogates, particularly when employing humans or primates as their subjects
(g) Toxin and bioregulator packaging and other processes to facilitate their delivery to specific targets within the human body.
D. *Combinations of indicators*
Reports of activities in which more than one of these indicators was evident.

activities of potential concern. Due to temporal and human resource limitations, we have not explored in similar depth the contextual factors that are important in understanding motivation behind State research and associated activities of potential concern. In the light of the caveats noted earlier, and given the widely acknowledged difficulties with determining intent with regard to dual-use research explored in Sect. 1.4, this publication does not purport to establish whether the specific illustrative activities highlighted in the country case studies have breached the BTWC or CWC. Instead, it attempts, through these studies, to highlight examples of research and associated activities that are of potential concern or could be misconceived as being of potential concern. The book subsequently makes associated recommendations as to how the State in question could seek to increase transparency and understanding of the true nature of those research activities.

Prior to publication, repeated attempts were made to contact the BTWC and CWC Permanent Representatives of the States detailed in the country case studies to provide them with an opportunity for clarification; substantive responses are cited in the case studies as appropriate and full copies of the relevant correspondence are contained in an Appendix.

CHAPTER 2

Dual-Use Chemical and Life Science Research of Potential Concern

2.1 What Is Happening in the Life Sciences?

The discovery in the middle of the last century that deoxyribonucleic acid (DNA) was at the centre of the mechanism of heredity, and through ribonucleic acid (RNA), the director of protein synthesis in living cells, was the foundation of the revolution in the life sciences and the advances in biotechnology that developed at an increased rate towards the end of the century. This revolution was bound to have significant implications for society as a whole. Importantly for this study, at the turn of this century, Matthew Meselson, Professor of Molecular Biology at Harvard University, suggested that as all previous scientific and technological revolutions had been applied in major ways to hostile purposes, it is probable that the same would happen to the revolution in civil biotechnology unless we found ways to prevent that happening. He thought that this would be a decades-long process, stating that:

> During the century ahead, as our ability to modify fundamental life processes continues its rapid advance, we will be able not only to devise additional ways to destroy life but will also become able to manipulate it—including the processes of cognition, development, reproduction and inheritance….

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_2

> Therein could lie unprecedented opportunities for violence, coercion, repression, or subjugation.[1]

Science and technology can advance in different ways: by narrowing the focus and digging ever deeper into a particular topic to elucidate its finer details, or by bringing together very diverse knowledge and techniques from quite different fields in order to develop new concepts and methods. Both approaches are necessary for rapid progress, but the second way, which has become known as 'convergence', is more likely to generate unexpected and potentially revolutionary changes. The international biological and chemical weapons expert, Ralf Trapp, explained, that certainly seems to be what is producing the revolutionary developments in the life sciences. He noted that:

> An example of convergence is the 'omics'—studies of all constituents collectively of a set of data/biomolecules such as genes (genomics), lipids (lipidomics), RNA (transcriptomics), proteins (proteomics), metabolites (metabolomics), the brain's structural and functional connections (connectomics) the cellular systems of an organism (cytomics) and more.[2]

Such advances, as he explained:

> have made it possible to edit genetic instructions, providing the tools for correcting genetic defects or directing organisms to produce molecules that are alien to them.… *At the same time, advances in bioinformatics, stimulation and modelling help scientists understand how biological systems work and how their processes can be augmented, interrupted or otherwise interfered with.* (Emphasis added)

And, of course, capabilities for the biological production of chemical agents are also adding to chemists' already formidable capacity for manufacture by more traditional methods. This augmentation of capabilities is having an effect across the whole of the life sciences and certainly in the work on toxins and bioregulators that is the subject of this

[1] Meselson, M. (2000) Averting the hostile exploitation of biotechnology. *The Chemical and Biological Weapons Conventions Bulletin*, **48**, 16–19. p. 16.

[2] Trapp, R. (2018) Convergence of Chemistry and Biology, and Nanotechnology, Chapter 7 in M. Crowley, et al. (Eds.) *Preventing Chemical Weapon; Arms Control and Disarmament as the Sciences Converge.* Royal Society of Chemistry, London. p. 195.

publication. For example, as a review in 2020 noted,[3] there have been significant changes in our understanding of the constituents and functions of animal toxins thorough the application of these novel methods in recent years. Indeed, the review noted that "[R]ecent advances in proteomics and transcriptomics have now made it possible to rapidly elucidate the venom proteome of even miniature venomous animals." Of course, this work is being done for reasons of basic understanding and for drug discovery, but there are obviously possible dual-use implications of at least some of such work.

The impact of the convergences of previously unrelated modern sciences and technologies (such as nanotechnology, artificial intelligence [AI], and machine learning) with the life sciences are often difficult to predict but can be highly significant. A dramatic illustration of the extremely problematic potential consequences of the malign application of such convergent processes was provided by a presentation at the Swiss Federal Institute for Nuclear, Biological and Chemical Protection at their biannual meeting on convergence in late 2021.[4] The presenters were civil scientists who build "machine learning models for therapeutic and toxic targets to better assist in the design of new molecules for drug discovery" and normally use "machine learning model predictions of bioactivity for the purpose of finding new therapeutic inhibitors of targets for human disease". For the purpose of the meeting, however, instead of the computer model penalising toxicity, they altered it so that it rewards both toxicity and bioactivity. To narrow the range of predictive molecules generated, they chose to drive the model towards compounds like the nerve agent VX. Within 6 hours over 40,000 virtual molecules were generated, and many of these were predicted to be more toxic than publicly known chemical warfare agents. Consequently, they warn that "[B]y inverting the use of our machine learning models, we had transformed our innocuous generative model from a helpful tool of medicine to a generator of likely deadly molecules." They also point out that while their experiment was focused on VX-like molecules, "it is equally applicable to other toxic small molecules with similar or different mechanisms, with minimal adjustments

[3] Herzig, V. et al (2020) Animal toxins—Nature's evolutionary-refined toolkit for basic research and drug discovery. *Biochemical Pharmacology*, **181**, 114096. https://doi.org/10.1016/j.bcp.2020.114096. p. 2.

[4] Urbina, F. et al. (2021) Dual use of artificial-intelligence-powered drug discovery. *Nature Machine Intelligence*, **4**, 189–191.

to our protocol." And they ask just how many people around the world have the know-how to do this kind of work and produce AI-designed molecules with predicted toxicity "many orders of magnitude more toxic than VX"? An important open question is just how significant a change has the development of these new capabilities actually brought to the social implications of the life and associated sciences?[5]

2.2 A Game Changer for Toxin Weapons Development?

Toxins are covered by the Biological and Toxin Weapons Convention for the very good reason that it was known at the time of the Convention's negotiation in the 1970s that certain natural toxins such as botulinum toxin and staphylococcal enterotoxin B (SEB) could be, and had been, weaponised effectively. Another factor was that the work on toxins had often been undertaken in conjunction with (or associated with) work on the microorganisms involved. As the BTWC covered development and production, part of the negotiators' thinking was that it would be difficult to distinguish between weapons laboratories and other facilities solely working on toxins and those working solely with microorganisms. So, if one wanted to have some degree of certainty that the ban on biological weapons was working, it made sense to include toxins within the scope of coverage. Moreover, at the time, the inclusion of toxin development in the scope of the BTWC may have appeared to make practical sense as such activities required different capabilities and were undertaken in different facilities than those associated with other "more traditional" chemical weapons. Furthermore, as long ago as the 1980s, when the possibilities of genetic engineering first clearly emerged, there were additional concerns that such new techniques could be used to produce large quantities of toxins through the insertion of genes for these toxins into bacteria that could be easily grown on an industrial scale. The Second BTWC Review Conference in 1986 agreeing that:

[5] See Kostal, M. E. (Ed.) (2020) *Disruptive and Game Changing Technologies in Modern Warfare: Development, Use, and Proliferation*. Springer Nature, Cham, Switzerland.

> Consequently, toxins (both proteinaceous and non-proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered.[6]

It was well understood that natural toxins have evolved though a millennia-long 'arms race' between the toxin producer (be they bacteria, virus, fungi, plant, or animal) and the toxin victim, and therefore this had resulted in toxins of great specificity with regard to the effected victims, and with fatal or incapacitating effects at low dosages. These characteristics could make such toxins attractive for those seeking agents to weaponise, particularly if the toxin was relatively easy to produce.

During the 1990s as the revolution in biotechnology progressed and the mechanism of action of some toxins were elucidated it also became possible to consider taking fragments of different toxins and recombining them to produce novel toxins with new functional properties. This might be done for benign purposes, for example, to treat cancer. This was highlighted in the UK's contribution to the review of relevant science and technology for the Fourth Review Conference of the BTWC in 1996 where it stated that:

> Much more is now known about the structure-function relationship of various toxin groups. The combination of electrochemical and other **biophysical techniques with molecular** biology approaches is expected to lead to the resolution of the molecular mechanisms of cell penetration by protein toxins. There is now a substantial amount of research on hybrids of toxins and toxin subunits with antibodies and viruses, often with the long-term objective of specifically destroying diseased cells such as cancer cells. In this type of therapy an antibody-toxin complex would be injected into the blood stream; the antibodies **attach** to receptors on the target cells which are subsequently eliminated by the action of the toxin, **while** healthy cells elsewhere in the body are unaffected.[7] (Original emphases)

[6] Dando, M. R. (1994) *Biological Warfare in the 21st Century: Biotechnology and the Proliferation of Biological Weapons.* Brassey's, London. Chapter 4, Efforts to Control to 1991. p. 74.

[7] Secretariat (1996) *Background Paper on New Scientific and Technological Developments Relevant to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction.* BWC/CONF. IV/4*, United Nations, Geneva. 30 October. p. 11.

Unfortunately, it was also not difficult to see how such developments might be put to hostile purposes, for example, by joining together fragments of different toxins to produce agents with unusual modes of action and effects.[8] Thus, at the turn of the century, Petro and his colleagues[9] raised the general question of whether a fundamental change in biological weapons development was then, or would be in the future, taking place? They stated that these:

> Emerging biotechnologies likely will lead to a paradigm shift in BW agent development; future biological agents could be rationally engineered to target specific human biological systems at the molecular level.

In this new paradigm, instead of focusing just on easily discoverable agents, and then either employing them directly or attempting to modify them, the biological weapons developer would increasingly be able to focus on the discovery of new biological targets in humans (or indeed animals or plants) to attack with bespoke biological agents designed to achieve ever more specific effects. Consequently, given the multiplicity of physiological systems that would become susceptible to attack, the biological weapons developer would inevitably have a long period of domination over those attempting to protect target populations, being able to employ new advanced biological agents if an arms race broke out in this area. So, our question here is what has happened in the study of toxins and does that suggest that the concerns raised by Petro and his colleagues apply in regard to potential novel toxin weaponry? Of particular relevance in this regard has been the contemporary advance of the systems biology approach[10] of combining experimental work with mathematical modelling and the use of information technology, so as to substantially increase the capabilities of researchers to predict the effect of novel chemicals on the physiological operations of living organisms.

[8] Dando, M. R. (2001) *The New Biological Weapons: Threat, Proliferation and Control*. Lynne Rienner, Boulder. Chapter 4, Toxins. pp. 45–66.

[9] Petro, J. B. et al. (2003) Biotechnology: Impact on biological warfare and biodefense. *Biosecurity and Bioterrorism*, **1**, 161–168. p. 162.

[10] Nixdorff, K. (2020) Developments in systems biology: implications for health and biochemical security, *The Nonproliferation Review*, 27(4–6), 459–473.

2.3 Toxicology as Part of the Biotechnology Revolution

We are concerned here with just a part of the huge field of modern toxicology (i.e. the study of the adverse effects of chemicals on living systems and the means to prevent or ameliorate such effects), specifically that relating to toxins. However, it is first necessary to set this in the context of the development of toxicological research as part of the rapid and enormous growth of the life sciences after World War II. The Society of Toxicology was inaugurated in 1961, and toxicologists were heavily involved, for example, in scientific risk/benefit analyses that have underpinned efforts to safely regulate the use of the enormous number of new chemicals that have been produced during that time.[11] The impact of the biotechnology revolution on toxicology was the subject of a major review in the Society of Toxicology's journal *Toxicological Sciences* in 2018. Titled "From Classical Toxicology to Tox21: Some Critical Conceptual and Technological Advances in the Molecular Understanding of the Toxic Response Beginning from the Last Quarter of the 20th Century", the paper noted that:

> Many genes important in cellular protection and metabolism of toxicants [chemicals with toxic effects] were cloned and characterized in the 80s, and gene expression studies became feasible, too. The development of transgenic and knockout mice [animals with some of their genes altered, or removed, by the experimenters] provided valuable animal models to investigate the role of specific genes in producing toxic effects of chemicals or protecting the organism from the toxic effects of chemicals.

And the authors continued:

> Further developments in toxicology came from the incorporation of the tools of "omics" (genomics, proteomics, metabolomics, interactomics), epigenetics [the study of the mechanisms of control of the operations of genes], systems biology, computational biology, and *in vitro* biology.[12]

[11] McCellan, R. O. (2020) Critical Reviews of Toxicology: Celebrating 50 Years of Publishing Scientific Advances in Toxicology and Risk Analyses. *Critical Reviews in Toxicology*, **50**(10), 827–835.

[12] Choudhuri, S. et al. (2018) From Classical Toxicology to Tox21: Some Critical Conceptual and Technological Advances in the Molecular Understanding of the Toxic Response Beginning From the Last Quarter of the 20th Century. *Toxicological Sciences*, **161**(1), 5–22. p. 5.

Table 2.1 Stages in the evolution of modern toxicology

From 1930s to the 1980s	The focus of toxicological studies evolved from identifying target organs of chemical toxicity to identifying targets of toxicity at an increasingly finer level of cellular organisation.
Beginning in the 1980s	Cloning and characterisation of genes associated with cellular protection and biotransformation of xenobiotics (chemicals from a different species, e.g. a predator), along with the availability of techniques to study gene expression, brought about a transformation of experimental toxicology.
Mainly in the 1990s	The development of more advanced gene expression techniques allowed more comprehensive study of the effect of a toxicant on the transcriptional regulation of multiple gene targets [how the toxic chemical affected the operation of the genes of the target organism] and the availability of various transgenic and gene knockout mice enabled the study of the functions of specific genes in mediating cellular toxicity and metabolism.
In this century	The role of epigenetic changes (alterations in gene expression or function rather than in the genetic code) in mediating toxicity, the data explosion and the development of genome editing tools has further transformed the capabilities of toxicologists.

From reference 51

Table 2.1 illustrates how our growing understanding of molecular biology impacted toxicology through some of the stages set out in the paper

The framework for understanding toxins and their effects had therefore expanded enormously: the toxic chemical's entry into the living organism was understood to produce an attempt by the physiological systems—right back to the genetic apparatus—to deal with the intrusion. So, it is within this framework of transformation of the whole of toxicology that research on toxins of concern here has to be understood.

2.4 Example 1: Botulinum Toxins

Botulinum toxins, which are produced by spore-forming anaerobic Gram-positive bacteria of the genus *Clostridium*, are considered by military medical experts and toxicologists to be "the most poisonous substances known" having an LD_{50} (i.e. dose that would be lethal to 50% of the exposed population) of approximately 1ng/kg.[13] Thus, it was not surprising that botulinum toxins were weaponised in the State-level offensive programmes of the last century. Today, they are also of concern in regard

[13] Middlebrook, J. L. and Franz, D. R. (1997) Botulinum Toxins, Chapter 33 in F.R. Sidell, et al. (Eds.) *Medical Aspects of Chemical and Biological Warfare*, Office of the Surgeon General, US Army, Washington, D.C. p. 647.

to bioterrorism,[14] particularly as there have been medical and cosmetic applications which have made the toxin much more accessible.

There are a number of botulinum toxins, classically considered to be of seven serotypes (A-G), but they all act by inhibiting the release of the neurotransmitter acetylcholine at neuromuscular junctions and thus causing a relaxation and paralysis of our muscles which in turn can result in death. Intensive study has elucidated the stages of the mechanism by which these protein toxins act through their different domains to disrupt the release of the neurotransmitter: the binding domain attaching the toxin to the surface of the nerve cell; the translocation domain getting the toxin into the cell; and the enzymatic domain splitting the peptide bonds in the proteins necessary to release the neurotransmitter.

In addition to the now established and widespread use of botulinum toxins in the cosmetics industry, research into these toxins and their action on human peripheral neuromuscular junctions is increasingly being applied to an ever-broader range of clinical applications. A recent review of their biology, pharmacology, and toxicology[15] listed seven widely different current clinical uses as shown in Table 2.2.

As would be expected from the previous part of this section, these toxins have also been the subject of applications of modern biotechnology techniques. As pointed out in 2018:

> BoNT [botulinum neurotoxin] classification remained stagnant for the last 50 years until, via bioinformatics and high-throughput sequencing techniques, dozens of BoNT variants, novel serotypes as well as BoNT-like toxins within non-clostridial species have been discovered… the now 'blooming field' of botulinum neurotoxin may shed light on their evolutionary origin and open exciting avenues for future therapeutic applications.

While these are the most lethal chemicals known, it turns out that the specificity of their activity, reversibility and limited diffusion after local application have made them safe and effective in medical applications. Moreover, as these authors point out: "An important aspect of BoNTs is their protein nature and, in general, the possibility to be easily engineered and produced by recombinant methods."

[14] Janik, E. et al. (2019) Biological Toxins as the Potential Tools for Bioterrorism. *International Journal of Molecular Sciences*, **20**, 1181: doi:10.3390/ijms20051181. pp. 3–5.

[15] Pirazzini, M. et al. (2017) Botulinum Neurotoxin: Biology, Pharmacology, and Toxicity. *Pharmacol Rev*, **69**, 200–235. p. 200.

Table 2.2 Clinical applications of botulinum neurotoxins

1. Dystonias
2. Spasticity
3. Autonomic disorders
4. Urologic pathologic conditions
5. Pain
   a. Neuropathic pain
   b. Primary headaches
6. Other applications
   a. Gastroenterology and proctologic disorders
   b. Depression
7. Cosmetic uses

From reference 52

And, more generally, that:

> these studies show how a few substitutions in amino acid sequence can functionally affect BoNTs biological activities, and how versatile BoNTs are to generate novel toxins with new and improved pharmacological features. In this direction, future structural and biochemical data on both the newly discovered serotype BoNT/X as well as on botulinum-like toxins, such as BoNT/Wo and BoNT/En, may open exciting avenues for original and currently unexpected therapeutic applications for human diseases.[16]

It has also become clear that BoNTs have effects at non-cholinergic synapses[17] and can have central nervous system (CNS) effects both of which might well lead to new therapeutic advances. Moreover, the central effects are also being exploited in research on the functions of the CNS of model organisms.[18] As Cesare Montecucco, one of the leaders of BoNT research, responded in reply to a 2018 interview question about why he was optimistic about the future of toxin and venom research in general, and thus also to his own special field of BoNT research:

[16] Tehran, D. A. and Pirazzini, M. (2018) Novel Botulinum Neurotoxins: Exploring Underneath the Iceberg Tip. *Toxins*, **10**, 190; doi:10.3390/toxins10050190. pp. 1, 9, 10.

[17] Anandan, C. and Jankovic, J. (2021) Botulinum Toxin in Movement Disorders: An Update. *Toxins*, **13**, 42; doi.org/10.3390/toxins13010042. p. 19.

[18] Caleo, M. and Restani, L. (2018) Exploiting Botulinum Neurotoxins for the Study of Brain Physiology and Pathology. *Toxins*, **10**, 175; doi:10.3390/toxins10050175.

> There are so many biological aspects of predator/prey or of host/pathogen interactions! And such a large variety of venom components and virulence factors! Not to forget the interactions and synergies among venom components and virulence factors that is almost unexplored.[19]

Added to that, of course, is the strong likelihood of rapid advances through convergence with other areas of the life sciences, for example, in *de novo* protein design,[20] protein toxicity prediction using neural networks;[21] and finally, the use of zebrafish as a novel and very different model toxicity testing organism.[22] In short, it seems clear that this very active area of toxin research will continue for some time. It is not possible to foresee if any of these advances will necessarily open up new potentialities for malign applications, but it is important to stress the overall significance of these developments because we are moving towards a systematic understanding across the whole range of toxins and their interaction with the regulation of the physiology of living organisms. This, as Petro and his colleagues noted, could allow the mechanistic development of novel agents for hostile use. While this first example of such radical developments is focused on the specific nature of the action of botulinum toxin, the second example throws the focus onto the organism's reaction to a toxin, in order to understand further the range of potential concern.

2.5 Example 2: Staphylococcal Enterotoxins

Staphylococcal enterotoxin B (SEB) is one of the more than 20 enterotoxins (a toxin produced in, or affecting, the intestine) produced by *Staphylococcus aureus*, a Gram-positive bacterium that causes illnesses worldwide.[23] The bacterium is carried by significant percentages of the human population either persistently (20%) or intermittently (60%). It is

[19] Holford, M. and Rummel, A. (2018) An Interview with Cesare Montecucco. *Toxins*, **10**, 307; doi:10.3390/toxins10080307. p. 5.

[20] Huang, P-S. et al. (2016) The coming age of *de novo* protein design. *Nature*, **537**, 320–327.

[21] Jain, A. and Kihara, D. (2019) NNTox: Gene Ontology-Based Protein Toxicity Prediction Using Neural Network. *Scientific Reports*, **9**, 17923; doi:10.1038/s41598-019-54405-6.

[22] Horzmann, K. A. and Freeman, J. L. (2018) Making Waves: New Developments in Toxicology with the Zebrafish. *Toxicological Sciences*, **163**(1), 5–12.

[23] Pinchuk, I. V. et al. (2010) Staphylococcal Enterotoxins. *Toxins*, **2**, 2177–2197; doi:10.3390/toxins2082177.

an opportunistic pathogen that secretes a wide range of enzymes that render the host's constituents into the nutrients it needs to grow, but it also produces enterotoxins that subvert the host's immune system at very low doses. The bacterium is often the cause of food poisoning, diarrhoea, and gastrointestinal injury. SEB was of interest as an incapacitating biological warfare agent (BWA) during the early Cold War because, in addition to being effective at low doses, it was relatively easy to produce and stable in dissemination as an aerosol. After inhalation there could be shortness of breath and chest pains which would last for some hours after exposure, whilst heavier doses could lead to fever, pulmonary oedema, and septic shock.[24]

The utility of the toxin was demonstrated in a test carried out in the US biological weapons programme in 1968.[25] In this trial (DTC Test 68-50) the agent used was codenamed PG (Staphylococcal enterotoxin B). The agent was released by a jet plane along a 40–50 km downwind grid. This single weapon use was "calculated to have covered 2,400 square km, producing 30% casualties for a susceptible population under the text conditions". The animals tested were caged monkeys which we now know have very similar responses to SEB as humans. The toxin is of considerable concern in regard to both State and non-State actor biological weapons today and consequently has been intensively studied by defence establishments to find effective countermeasures. A 2013 paper by scientists from the UK Defence Science and Technology Laboratory (at Porton Down) stated that:

> The sensitivity of humans to the incapacitating effects of SEB makes the agent of significant concern to both military and civilian target populations, particularly from a terrorist and larger scale biological warfare perspective and consequently features on threat lists in both the United Kingdom and in the United States. In particular, its efficacy as an incapacitant at very low doses may lower the threshold for its use in warfare.[26]

[24] Pinchuk, I. V. et al. (2010), op. cit. pp. 2186–2187.

[25] Regis, E. (1999) *The Biology of Doom: The History of America's Secret Germ Warfare Project*. Henry Holt, New York. pp. 201–204.

[26] Lindsay, C. D. and Griffiths, G. D. (2013) Addressing bioterrorism concerns: Options for investigating the mechanism of action of *Staphylococcus aureus* enterotoxin B. *Human and Experimental Toxicology*, **32**(6), 606–619. pp. 606–607.

And the paper also noted that concerns regarding SEB "are compounded by the lack of effective medical countermeasures… for mass treatment of affected populations". A military review of toxins of concern in 2016 also commented[27] that "[C]urrently there is no available antidote or preventive vaccine, although there are several ongoing attempts at vaccine development, still in preliminary stages."

We can recognise a similar impact of modern biotechnology methods on our understanding of the mechanism of SEB's actions as we saw in regard to BoNTs. It was known from the end of the nineteenth century that certain bacteria could induce fever in those affected. However it was not until the late 1980s that the toxins they produce were recognised as being super antigens (i.e. substances that result in excessive activation of the immune system of their targets).[28] And it was only in the past few decades that the mechanisms involved were effectively elucidated. From the point of view of this study what is of most interest is that in this example, we can focus on the response of the living organism to the toxic chemical (i.e. SEB). We have already noted that the response can involve many parts of the physiological system right back to the fundamental genetic control elements of the cell. So, we can now begin to see the cells of the organism as components of a 'chemical machine' able to carry out a variety of functions and that these functions can be coordinated by chemical messengers of the organism—that is, bioregulators. These bioregulators include the hormones of the endocrine system, neurotransmitters and neuromodulators of the nervous system, and cytokines of the immune system.

In this example, SEB causes its deleterious effects by triggering the over-expression of the natural immune response of the body. The mechanism by which SEB subverts the normal complex feedback control mechanisms—normally mediated by the relevant bioregulators (cytokines)—of the immune system of the body has now been established. The cells of the immune systems are normally activated to combat the invading disease-causing organism when surface proteins on these organisms or their toxins attach to specific sites on the defending cells. However, SEB subverts this

[27] Berger, T. et al. (2016) Toxins as biological weapons for terror—characteristics, challenges and medical countermeasures: a mini review. *Disaster and Military Medicine*, **2**(7); DOI 10.1186/s40696-016-0017-4. pp. 3–4.

[28] Krakauer, T. (2019) Staphylococcal Superantigens: Pyrogenic Toxins Induce Toxic Shock. *Toxins*, **11**, 178; doi:10.3390/toxins11030178. p. 2.

normal system by utilising a different attachment point and not the normally regulated attachment points of the defending cells:

> Staphylococcal superantigens hyperactivate cells of the innate immune system and adaptive T-cells concomitantly by binding to the major histocompatibility complex class II (MHC II) molecules on antigen-presenting cells (APCs) and specific Vβ regions of T-cell receptors (TCRs). However, their mode of interaction differs from conventional antigens in that they bind on the outside of the peptide-binding groove of MHC II and exert their biological effects as an intact molecule without being 'processed' by APCs.

And as this 2017 paper adds:

> The bridging of superantigens to MHC II and TCR allows cooperative interactions between receptors, hyperactivating the host immune system. Two decades of elegant structural and molecular studies defined binding motifs of bacterial superantigens with MHC II and TCRVβ.[29]

This bypassing of the normal immune reaction results in the overproduction of cytokines causing a 'cytokine storm'. This, in turn, results in the incapacitating effects upon the body that the toxin is seen to exert.

For good medical reasons the details of the complex pathways in the immune system through which the effects are brought about are being intensively studied. This research might reveal specific points in the pathways which could be blocked by new drugs,[30] to thereby regulate the system when it has ceased to function normally. However, our growing understanding of these pathways also opens up the possibilities of new targets that might be open for attack. Again, as in our first example, it is not possible to know whether these advances will lead to the malign applications, for example, in demonstrating other means by which the immune system could be subverted, but it would be sensible to keep that possibility in mind. We turn now to our third example to emphasise the point about the dangers of the malign manipulation of the organism's chemical machinery via its bioregulators.

[29] Krakauer, T. (2017) FDA-approved immunosuppressants targeting staphylococcal superantigens: mechanisms and insights. *Immuno Targets and Therapy*, **6**, 17–29. pp. 17–18.

[30] Horn, C. M. and Kielian, T. (2021) Crosstalk Between *Staphylococcus aureus* and Innate Immunity: Focus on Immunometabolism. *Frontiers in Immunology*, **11**; doi:10.3389/fmmu.2020.621750.

2.6 Example 3: Bioregulators

In Chap. 1 we noted that the World Health Organization, in the 2004 Second Edition of its *Public Health Response to Biological and Toxin Weapons*, stated that the word 'toxin' in the Biological and Toxin Weapons Convention includes substances—like histamine—which scientists would see as bioregulators.[31] The reason for this inclusion should now be clear: what a lethal or incapacitating toxin often does is to disrupt *indirectly* the normal bioregulatory system of the victim; the hostile use of a bioregulator does the same thing *directly*. So, botulinum toxin interferes with the normal functions of the neurotransmitter acetylcholine, and SEB interferes with the normal operations of the cytokine bioregulators of the immune system, in contrast the histamine of the wasp sting directly adds unusually large amounts of the bioregulator to an unusual place. All living organisms have similar components in their physiological systems. So, an attacking organism (such as the wasp) utilising a natural bioregulatory weapon (histamine in its sting) would likely have access to substances that could be moulded over evolutionary time to closely fit and affect bioregulatory systems in its target. This is also true of certain predators employing venom (which are in effect bioregulators) against their prey. For example, sarafotoxins of viper venoms have a very similar structure and action to the natural vasoconstrictor endothelins found in its potential victims.[32]

It should be of little surprise, therefore, to see concerns voiced by certain States about the possible misuse of certain natural bioregulators for malign purposes. For example, a 1999 experimental study by the Swedish Defence Research Establishment (FOA)[33] investigated the tachykinin Substance P, which is a bioregulator with many different functions in mammals. The FOA study, which used guinea pigs as animal test subjects, found that inhalation of an aerosol of Substance P caused acute toxicity in these subjects. The authors warned that if Substance P was aerosolised, "it could, at extremely low air concentrations, result in incapacitation among

[31] World Health Organization (2004) *Public Health Response to Biological and Chemical Weapons*. 2ND edition, WHO, Geneva. p. 216.

[32] Dando, M. R. (2006) *The New Biological Weapons: Threat, Proliferation and Control*. Lynne Rienner, Boulder, Colorado. See Chapter 5 Bioregulatory Peptides: ENDOTHELIN. pp. 68–73.

[33] Koch, 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**, 19–23. p. 22.

humans." The agent used in this way would cause intense breathing problems, and as Substance P is important in the pathology of fatal asthma, the mechanisms involved are also being intensively studied to find means of treating this respiratory disease.[34]

Another startling example concerns the bioregulator neuropeptide orexin that was only discovered at the end of the last century and found to be a key element in controlling the sleep/wake cycle. Indeed, it quickly became clear that loss of the orexin producing cells in the brain, most likely by a process of autoimmunity, was sufficient to cause Type 1 Narcolepsy with the characteristic feature of cataplexy (sudden loss of muscle tone).[35] Clearly having the ability to cause cataplexy might be attractive to those with hostile intentions and of great concern to those who might be affected. Work on the orexin system led in a remarkably short time to an antagonist drug, inhibiting the effect of orexin, that was approved for use to help people with insomnia. It also rapidly became clear that the orexin neurotransmitter played a role in a wide range of other body systems such as appetite and energy balance.

Little wonder then that the World Health Organization's 2021 horizon scan of dual-use concerns in relation to global public health viewed the misuse of bioregulators as being an issue of immediate concern, stating that:

> While the potential misuses of bioregulators have been known for decades, discoveries in neuroscience and neurochemistry mean that bioregulators could be used for more targeted, hostile purposes, including damage to the central nervous system, soldier enhancement, crowd suppression and behaviour manipulation.[36]

In the longer term (a decade and more ahead) this horizon scan raised dual-use concerns about neurobiology advances in general:

[34] Hodo, T. W. et al. (2020) Critical Neurotransmitters in the Neuroimmune Network. *Frontiers in Immunology*, **11**, Article 1869, doi:10.3389/fimmu.2020.01869. pp. 11–13.

[35] Dando, M. R. (2020) *Neuroscience and the Problem of Dual Use: Neuroethics in the New Brain Projects*. Springer Nature, Switzerland. See Chapter 4 Dual Use Neuroscience. pp. 53–71.

[36] World Health Organization (2021) *Emerging technologies and dual-use concerns: a horizon scan for global public health*. WHO, Geneva, October. p. 6.

> Of particular concern is neuroscientific research into assessing or modifying human thought, emotions and actions and means to affect the nervous system and alter cognitive states, behaviour and functions for performance enhancement and degradation. This broad topic overlaps substantially with other issues raised in this horizon scan. For instance, nano-technological delivery could erode one of the main barriers to the use of agents that act on the central nervous system. *Similarly, understanding of the neurological function of bioregulators could provide another means of exploiting neurological advances for hostile purposes.* (Emphasis added)[37]

It seems likely that there are many, many, more peptide bioregulators to be discovered, and much to be revealed about the functions of the known and currently unknown bioregulators. We can get an idea of the radical nature of the likely advances from a review of progress in neuroimmunology research (i.e. research on the links between the nervous and the immune system).

2.7 Advances in Neuroimmunology

Steven Greenberg's *Concise History of Immunity* ends in the 1990s with speculation on the future 20–30 years of developments in immunology. Understandably, he suggested that the research would continue to reveal more and more of the molecular mechanisms involved in the immune response through the use of novel technologies:

> Further advances in the cell biology of the immune system will no doubt occur, which will lead to novel vaccines for infectious and non-infectious diseases, such as cancer and diseases of aging. New receptor- or cytokine-modifying therapeutics will be developed, based on insights obtained from experimental immunology…

And he further underlined the significant benign applications of these new technologies:

> The application of the human genome project [the project that first described the human genome earlier in this century] to diseased populations will identify new drug targets, and high-throughput screens and combinatorial chemistry will accelerate the pace of drug discovery. Gene and protein

[37] World Health Organization (2021) op. cit. p. 8.

> microarray techniques and proteomics will reveal new components of immunity that will expand our knowledge of how the immune system works.[38]

This process has been particularly clear in regard to neuroimmunology, as can be seen in a series of reviews published recently some 20 years later. Progress in this field had previously been held back by the dogma[39] that asserted that the brain was relatively isolated from the immune system by the blood-brain barrier. In short, this view held that the nervous system was relatively little connected with the functions of the immune defence system's operations in the rest of the body. However, as Gruol, the editor of a set of papers noted in 2017:

> It is now widely accepted that an innate immune system exists within the brain and plays an important role in both physiological and pathological processes. This neuroimmune system is comprised of brain cells that produce and secrete chemicals that are historically considered signaling factors of the peripheral immune system, such as cytokines and chemokines.

Whilst the brain contains the neurons that carry out its coordination roles, it also contains many other types of cells, such as astrocytes and microglia—collectively called glia cells—that carry out a variety of different important functions within the brain. Gruol noted that:

> Cells of the brain, primarily glia cells…but also neurons under some conditions, produce a large number of immune factors. In addition, endothelial cells of the brain and peripheral immune cells that enter the brain can contribute to the immune environment of the brain.[40]

Another paper titled 'Maximising the potential of neuroimmunology' argued that while the interactions between the nervous system and the immune system in disease states had been recognised previously, it was now becoming clear that the immune system also played an important role

[38] Greenberg, S. (undated) A Concise History of Immunology. Available at http://www.columbia.edu/itc/hs/medical/pathophys?immunology/readings/ConciseHistoryImmunology.pdf..

[39] Nutma, E. et al. (2019) Neuroimmunology—the past, present and future. *Clinical and Experimental Immunology*, **197**, 278–293;doi:10.1111/cel.13279.

[40] Gruol, D. (2017) Advances in Neuroimmunology. *Brain Sci*, 7, 124; doi:10.3390/brainsci7100124. p. 1.

in brain development and homeostasis in a healthy body. The paper also stressed the importance of the new technological developments that could bring radical advances in our understanding:

> The field is now at a tipping point, able to make the most of the recent technological developments, such as mass cytometry, single cell RNA sequencing, 2-photon microscopy… and gene editing technologies.[41]

An example of the unexpected results of such research can be seen in work on the orexin system described in Sect. 2.6 of this chapter. What was not clear during earlier work on the orexin system in relation to the sleep-wake cycle is the more recent finding that it also had significant effects on the immune system. Work on this issue is still in an early stage but there are clear possibilities for the development of new therapeutics as can be seen from a recent review of such possibilities.[42] However, given the clear possibilities that the orexin bioregulator is involved not just in narcolepsy, but also in a variety of other processes, including, for example, neuroinflammation, malign dual-use applications cannot be ruled out. It will take some time for the details of these neuro-immunological mechanisms to be worked out and for new therapeutic drugs to be developed to manipulate these mechanisms, but there are clearly strong indications of success.[43] More generally it is clear that the further investigation of such interactions between the nervous system and the immune system will lead to a cornucopia of new knowledge[44]—that will be intended to be put to beneficial use, but which might also be subject to malign application. Moreover, advances in this field of research seem certain to accelerate after the COVID-19 pandemic because of the issue of "Long COVID."

[41] Caldwell, L. J. et al. (2020) Maximising the potential of neuroimmunology. *Brain, Behavior and Immunity*. https://doi.org/10.1016/j.bbi.2020.03.010. p. 2.

[42] Couvineau, A. et al. (2019) Orexins as Novel Therapeutic Targets in Inflammatory and Neurodegenerative Diseases. *Frontiers in Endocrinology*, **10**, Article 709; doi:10.3389/fendo.2019.00709.

[43] Becquet, L. et al. (2019) Systemic administration of orexin A ameliorates established experimental autoimmune encephalomyelitis by diminished neuroinflammation. *Journal of Neuroinflammation*, **16**, 64. https://doi.org/10.1186/s12974-019-1447-y.

[44] Nistico, R. et al. (2017) Synaptoimmunology—roles in health and disease. *Molecular Brain*, **10**, 26; doi:10.1186/s13041-017-0308-9.

2.8 The Impact of Long COVID

A key finding of this chapter's previous sections is that there has been, and will continue to be, a rapid increase in our understanding of the mechanisms by which toxins and bioregulators interact with the myriad, complex, and inter-connecting systems regulating the functions of living organisms, including human beings. It seems very likely that this process of intensive scientific investigation will accelerate after the COVID-19 pandemic because many people affected will also suffer from what has been called "Long COVID"—disturbances including of the nervous system that outlast the initial infection and disease for extensive periods of time. Thus, it seems certain that more funding will follow into the research that helps to elucidate the mechanisms by which this comes about and how it might be prevented or ameliorated.[45]

There is good reason to expect such detrimental health effects from a new virus, as previous outbreaks such as the Spanish Flu pandemic of 1918–1919 resulted in major long-term nervous disease problems.[46] In regard to COVID infections, a 2021 study has found that:

> Although most COVID-19 patients primarily develop respiratory symptoms, an increasing number of neurological symptoms and manifestations associated with COVID-19 have been observed…. Essential and common neurological symptoms including gustatory and olfactory dysfunctions, myalgia, headache, altered mental status, confusion, delirium, and dizziness.[47]

And the text notes the possibility of:

> neurological manifestations and complications that are of great concern such as stroke, cerebral (sinus) venous thrombosis, seizures, meningoencephalitis, Guillain–Barré syndrome, Miller Fisher syndrome, acute myelitis, and posterior reversible encephalopathy syndrome (PRES).

[45] Collins, F. S. (2021) *NIH launches new initiative to study "Long COVID."* Office of the NIH Director, Washington, D.C., 23 February.

[46] Stefano, G. B. (2021) Historical Insights into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID. *Medical Science Monitor*, **27**, e931447; doi:10.12659/MSM.931447.

[47] Harapan, B. N. and Yoo, H. J. (2021) Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). *Journal of Neurology*, https://doi.org/10.1007/s00415-021-10406-y. (p. 1).

Clearly, issues of this complexity are not going to be easily or quickly resolved and will need considerable new advances in our understanding of the underlying mechanisms. There appear to be at least four general mechanisms that will need to be thoroughly investigated:[48] the consequences of severe and sudden infection of the brain; a maladaptive overresponse from the immune system as it attempts to fight the infection; chaos in the body's other systems perhaps, for example, producing low oxygen levels; and blood-clotting abnormalities. The expected surge in life science research will, of course, be driven by benign intent and will hopefully bring significant advances for the benefit of current and future sufferers of 'Long COVID'. However, once again, the international scientific and disarmament communities should be sensitive to the potential dual-use implications of these research trajectories and ensure they are not employed for malign purposes.

2.9 Conclusions

A review paper published in 2019[49] gave a good picture of the extent of our modern understanding of the mechanism of action of toxins as set out in Table 2.3.

So, what we see here is a systematic overview of the whole field of toxin types and mechanisms—a knowledge base that could be used to develop advanced chemical/biological weapons agents, as Petro and his colleagues foresaw. The review also listed some of the key questions that are now the subject of intensive study, and thus pointing the way to the future of this area of research. These questions included: "[W]hat tools can be developed that will allow toxins with completely new mechanisms of action to be identified?"; "[H]ow can we easily mass produce emerging toxins with unique properties, but highly complex structures?"; and "[C]an peptide-based toxins be adapted or formulated in order to increase their longevity of action and targets within the body?" It will be evident that these questions are also not without significance to the problem of dual-use if you consider the kind of knowledge that would assist the weaponeer in the identification, modification, and production of novel weapons agents.

[48] Stevens, R. (2021) *How does coronavirus affect the brain?* John Hopkins Medicine Website. https://www.hopkinsmedicine.org/health.

[49] Clark, G. C. et al. (2019) Friends or Foes? Emerging Impacts of Biological Toxins. *Trends in the Biochemical Sciences.* **44**(4), 365–379. pp. 369, 376.

Table 2.3 A catalogue of toxin types and mechanisms

Superantigens	Short circuit the immune system (e.g. SEB)
Membrane-damaging	'Digest' the cell membrane (e.g. Gangrene toxin)
Large pore forming	'Punch holes in cell membranes (e.g. Streptolysin O)
A-B subunit	'Crash' cellular functions (e.g. Botulinum toxin)
'Chemical'	'Disable' cellular functions (e.g. Saxitoxin)
Small peptide ion channel binding	'Open or close' ion channels (e.g. Conotoxins)
Small cytolytic peptide	"Liquefy' cell membranes (e.g. bee venoms)
Venoms	'Cocktail' of components to act synergistically for quick action

From reference 89

In regard to bioregulators, in a recent essay, Solomon Snyder attempted to answer the question of how many different transmitters are there in the brain. He suggested that the numbers of well-known transmitters like amines (e.g. noradrenaline) and amino acids (e.g. glutamate and GABA) was not large.[50] But he pointed out that in contrast "there could exist many more peptides than is presently known." He suggested that all of these should be possible to identify with current technology and that "the number will be finite, perhaps no more than two hundred." However even that is quite a large number and each peptide identified could have diverse functions. And Snyder was only addressing neurotransmitters, the potential numbers of bioregulators yet to be identified in all other human physiological systems are currently unknown. It does, however, again demonstrate the enormous range of possibilities that could become available for the weaponeer of the future to explore, manipulate, and weaponise.

[50] Snyder, S. H. (2018) The Brain Harbors Many Neurotransmitters, pp. 88–93 in D. J. Linden (Ed.) *Think Tank: Forty Neuroscientists Explore the Biological Roots of Human Experience*. Yale University Press, New Haven. p. 92.

CHAPTER 3

The China Case Study

3.1 Historical Toxin Weapon Development

China acceded to the Geneva Protocol in 1952, to the Biological and Toxin Weapons Convention (BTWC) in 1984 and ratified the Chemical Weapons Convention (CWC) in 1997. On CWC ratification, China declared that it had previously conducted a small chemical weapons programme for offensive purposes, which it declared to have subsequently dismantled, as required under the Convention.[1] In its 29 October 2021 response to the authors' information request, the Chinese Permanent Mission to the OPCW stated: "China has faithfully fulfilled its obligations under the CWC and honored its commitments. China has submitted its various categories of initial and

The original version of this chapter was revised with a reference updated. The correction to this chapter can be found at https://doi.org/10.1007/978-3-031-10164-9_11

Following an information request by the authors, on 29 October 2021, the Chinese Permanent Mission to the OPCW provided information on issues covered by the case study. An additional response was provided on 2 November 2021 by the Permanent Mission of China to the UN in Geneva. Relevant extracts from these responses are incorporated in the case study and full versions of both responses are contained in an Appendix of this publication.

[1] Crody, E. (2002) China's Role in the Chemical and Biological Disarmament Regimes, *Non-Proliferation Review*, Spring, 16–47. p. 20.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_3

annual declarations to the OPCW in a timely and comprehensive manner pursuant to the provisions of the CWC."[2]

China has never acknowledged and in fact has repeatedly explicitly denied any previous toxin or other biological weapons development programmes. For example, in an October 2002 public statement announcing introduction of *Regulations on Export Control of Dual-use Biological Agents and Related Equipment and Technologies*, a government spokesperson declared "China has always fulfilled earnestly its obligations under the [BTWC] Convention. China has never developed, produced or stockpiled any biological weapons, and never assisted any country to acquire or develop these weapons."[3] In its 2 November 2021 response to the authors' information request, the Permanent Mission of China to the UN in Geneva stated that "[C]hina has all along implemented its obligations under the BWC…in a comprehensive and earnest manner."[4] The response makes reference to the Chinese Ministry of Foreign Affairs *Biological Weapons Convention Factsheet* which declares that

> the Chinese government has always advocated the complete prohibition and thorough destruction of all weapons of mass destruction, including biological weapons, and attaches importance to the positive role of the [BTWC] convention in maintaining world peace and security, and supports the purposes and objectives of the convention…China has always fully and conscientiously fulfilled its obligations under the convention. China formulates and strictly enforces relevant laws and regulations to ensure the effective implementation of the convention.[5]

[2] Qian Wang, First Secretary, Permanent Mission of the People's Republic of China to the OPCW, The Hague, Netherlands, response to an information request from the University of Bradford, 29 October 2021. Mr Wang also described measures China has undertaken to establish "the legal framework for the implementation of the CWC"; establish a "comprehensive regime of effective administration of the production, trading, use, stockpiling, import and export of scheduled chemicals" and "to prevent and prosecute acts that use substances like toxic chemicals to carry out terrorist activities." In addition, Mr Wang highlighted China's long-standing advocacy of "responsible scientific research", and its promulgation of "a series of domestic laws and regulations to regulate research activities." For further information see Appendix of this report.

[3] China (2002) *Spokesperson on the Introduction on the Regulations of the People's Republic of China on Export Control of Dual-use Biological Agents and Related Equipment and Technologies.* Ministry of Foreign Affairs, 17 October.

[4] Disarmament team, Permanent Mission of China to the UN in Geneva, response to an information request from the University of Bradford, received by email on 2 November 2021.

[5] China, Ministry of Foreign Affairs, *Biological Weapons Convention Factsheet*, previously available at biological weapons convention—ministry of foreign affairs of the people's republic of china (fmprc.gov.cn) (last accessed 2 November 2021).

China's 2 November 2021 response to the authors further highlighted the actions China has taken to "regulate the risk of biotechnology research and development", and "advocate…for responsible biological research".[6]

Although publicly available information is extremely limited, certain States and civil society observers have claimed that China previously conducted an offensive biological and toxin weapons research programme. For example, in its April 2022 report on *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitment [Arms Control Compliance Report]*, the US State Department stated: "The United States assesses that China possessed an offensive biological warfare program from 1950s to at least the late 1980s…. *As part of its historical BW program, the PRC [the People's Republic of China] had reportedly weaponized ricin, botulinum toxins,* and the causative agents of anthrax, cholera, plague, and tularemia" (emphasis added).[7] The US has repeatedly highlighted its long-running doubts as to whether the Chinese historical biological and toxin weapon development programme has been completely shut down. For example, the 2022 US State Department *Arms Control Compliance Report* stated: "[T]here is no available information to demonstrate that the PRC took steps to fulfil its treaty obligations under Article II of the BWC…to destroy or to divert to peaceful purposes all items specified in Article I of its past offensive BW program."[8] It should be noted that for the allegations the US makes, in the unclassified versions of the *Arms Control Compliance Reports* and *CWC Compliance Reports*, concerning Chinese toxin or bioregulator related activities of concern, no substantive verifiable supporting evidence is provided. It is not known whether such information is provided in the classified versions of such reports.

[6] Disarmament team, Permanent Mission of China to the UN in Geneva (2021) op. cit.

[7] United States (2022) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitment. State Department*, April. p. 35; for a similar analysis see: United States (2021) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitment. State Department*, April. p. 47; United States (2020) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, June, p. 57; United States (2019) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, August, pp. 45–46.

[8] United States Arms Control Compliance Report (2022) op.cit. p. 35.

In its response to the authors' information request, the Chinese Permanent Mission to the OPCW stated:

> As for the Compliance Report issued by the US State Department, I'd like to highlight the following points. In recent years, the US has been making up the so-called annual report on Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments, making wanton comments on other countries' arms control and non-proliferation policies while exalting its own 'exemplary' behavior. It is nothing but a threadbare ploy it uses to deflect international attention and malign other countries. The allegation against China is groundless. China has always been firmly opposed to this. I hope Bradford University is a responsible and objective research institution. I trust you and your team will conduct research based on credible materials, not quoting the reports that deliberately smear other States Parties for political purposes.[9]

3.2 Contemporary Dual-Use Toxin Research

China has a large and sophisticated civilian biomedical and biotechnological infrastructure that undertakes research and development and production activities for legitimate purposes. Chinese civil scientists have published a great deal of significant work on toxins and bioregulators, with potential dual-use applicability, for sound medical and scientific reasons, with no discernible involvement of defence institutions.[10] Furthermore, Chinese scientists based in defence facilities and in civil institutions, have conducted legitimate dual-use toxin research and published papers in conjunction with foreign counterparts. For example, a 2021 paper detailed work on the T-2 toxin[11] by scientists from Yangtze University and Nanjing Agricultural University with the University of Hradec Kralove, Czech Republic, and the Military Medical Academy in Belgrade, Serbia. T-2 occurs widely as a contaminant of food and crops and causes toxicity by diverse mechanisms. This work was funded in part by Chinese, Czech, and Serbian military sources.

[9] Qian Wang (2021) op. cit.

[10] See, for example, Zhang, Y. (2015) Why do we study animal toxins? *Zoological Research*, **36**(4), 183–222; Wang, X. et al. (2018) Molecular basis and mechanism underlying the insecticidal activity of venoms and toxins from *Latrodectus* spiders. *Pest Management Science*, **75**(2), 318–323.

[11] You, L. et al. (2021) Hypoxia, oxidative stress, and immune evasion: a trinity of the trichothecenes T-2 and deoxynivalenol (DON). *Archives of Toxicology*, **95**, 1899–1915.

On other occasions Chinese defence scientists have participated in larger international collaborations, such as when scientists from the Research Institute of Chemical Defence in Beijing contributed to OPCW biotoxin exercises for ricin.[12] Indeed, in its response to the authors' information request, the Chinese Permanent Mission to the OPCW noted that: "the detection and identification research on toxins has been carried out by many [CWC] States Parties and the SAB welcomed the efforts of the Technical Secretariat of OPCW to conduct biotoxin exercises in which two Chinese laboratories have also participated."[13]

However, certain States have raised concerns with regard to the potential for misuse of China's extensive research and biotechnology infrastructure—particularly those elements associated with Chinese military or other defence entities—in the development of toxin weapons. In its 2021 evaluation of China's compliance with the BTWC, the US State Department reported that "studies conducted at *PRC military medical institutions*… included information that discusses *identifying, testing and characterizing diverse families of potent toxins with dual-use applications*" (emphases added).[14] This US *Arms Control Compliance Report* consequently highlighted US "compliance concerns with respect to [such] Chinese military medical institutions' *toxin and biotechnology research and development because of the dual-use applications and their potential as a biological threat*" (emphasis added).[15]

Similar concerns regarding studies by researchers from Chinese military medical institutions to "identify, test and characterize diverse families of potent toxins" have been raised by the US in terms of China's compliance with the CWC. In 2021, the US State Department's report on CWC compliance stated that available information on these studies: "raises questions about the intended purposes of the work conducted by the researchers…. The United States is concerned about China's interest in … *toxins because these agents have utility for chemical weapons applications*"

[12] Liang, L-H. et al. (2021) Rapid Differential Detection of Abrin Isoforms by an Acetonitrile-and Ultrasound-Assisted On-Bead Trypsin Digestion Coupled with LC-MS/MS Analysis. *Toxins*, **13**, 358. https://doi.org/10.3390/toxins13050358.

[13] Qian Wang (2021) op. cit.

[14] United States *Arms Control Compliance Report* (2022) op. cit. p. 35; for a similar analysis see: United States *Arms Control Compliance Report* (2021) op. cit. p. 46; and United States *Arms Control Compliance Report* (2020) op. cit. p. 57.

[15] United States Arms Control Compliance Report (2022) op. cit. p. 35; for a similar analysis see: United States *Arms Control Compliance Report* (2021) op. cit. p. 47; United States *Arms Control Compliance Report* (2020) op. cit. p. 57; United States *Arms Control Compliance Report* (2019) op. cit. pp. 45–46.

(emphasis added).[16] Consequently, the US State Department concluded that "[B]ased on available information, *the United States cannot certify that China has met its obligations under the [Chemical Weapons] Convention due to concerns regarding* China's research of pharmaceutical based agents (PBAs) and *toxins with potential dual-use applications*" (emphasis added).[17]

The potential dual-use applicability of certain Chinese toxin research has been highlighted by individual US government CBW experts. For example, in July 2019, Dr James Madsen, lead clinical consultant and clinical laboratory director at the Chemical Casualty Care Division at the US Army Medical Research Institute of Chemical Defense (MRICD), stated that "China is the leader in toxin-based threats" and that "China knows more about marine toxins in particular than any other country in the world."[18] Official US perceptions of China's intentions in this area are unclear.

Civil society researchers have also raised concerns about China's dual-use research on toxins. In his 2015 study, Shoham—a former Israeli military intelligence officer and subsequently senior researcher at the Begin-Sadat Center for Strategic Studies—argued that China had utilised "'dual use' biotechnological and biomedical disciplines" as part of its attempts to obfuscate its biological weapons related activities. According to Shoham, this approach had been employed "at both the strategic and tactical levels, namely, within the organizational pattern of the BWP [biological weapons programme] run by China at large as well as in respect to various research, development and production projects conducted for specific objectives".[19] With regard to toxins, Shoham illustrated his concerns through examination of certain dual-use research undertaken by the International Joint Cancer Institute (IJCI) of the Second Military Medical University, in Shanghai. He highlighted IJCI investigations into the relationship between

[16] United States (2021) *Compliance with the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and their Destruction Condition (10) (c) Report*. U.S. Department of State, April pp. 10–11.

[17] United States CWC Compliance Report (2021) *op.cit*., p. 10.

[18] Tadjdeh, Y. (2019) CBRN Conference News: Defense Officials See Increased Threat from Chinese, Russian Chem-Bio Weapons (UPDATED). *National Defense Magazine*, 23 July.

[19] Shoham, D. (2015) China's Biological Warfare Programme: An Integrative Study with Special Reference to Biological Weapons Capabilities. *Journal of Defence Studies*, **9**(2), 131–156.

ricin's structure and its protein synthesis inhibitory mechanism,[20] a study of the neutralisation of botulinum toxin B by the synergistic action of antibodies recognising the protein and ganglioside receptor binding domain,[21] and research into the structural basis of the neutralising mechanism of antibodies against staphylococcal enterotoxin B.[22]

Whilst acknowledging the contested nature of Shoham's study, the current authors have identified additional ICJI ricin research of a potential dual-use applicability, including investigation of the neutralisation mechanism of mAb 6C2 antibodies against ricin.[23] Further relevant research by other Chinese medical institutes included preparation by researchers at the State Key Laboratory of Pathogen and Biosecurity, together with the Institute of Microbiology and Epidemiology, of egg yolk antibodies against botulinum toxin B and examination of their passive protection in mouse models.[24]

The current authors have identified further research by scientists at the Second Military Medical University that described their attempts to screen and identify novel toxins, that may have dual-use application of concern. This included a 2011 paper that described isolation of a new cytolysin from the sea anemone *Stichodactyla gigantea* which was found to possess high haemolytic activity to human red blood cells, and toxicity to the cardiovascular and respiratory systems of rats.[25,26] In addition a 2019 paper

[20] Dai, J. et al. (2011) Identification of a Novel Functional Domain of Ricin Responsible for its Potent Toxicity. *The Journal of Biological Chemistry*, **286**(14), 12166–12171.

[21] Chen, C. et al. (2012) Potent Neutralization of Botulinum Neurotoxin/B by Synergistic Action of Antibodies Recognizing Protein and Ganglioside Receptor Binding Domain. *PLoS One*, **7**(8), e43845.

[22] Xia, T. et al. (2014) Structural Basis for the Neutralization and Specificity of Staphylococcal Enterotoxin B against its MHC Class II Binding Site. *mAbs*, **6**(1), 119–29.

[23] Zhu, Y. et al. (2013) Structural Insights into the Neutralization Mechanism of Monoclonal Antibody 6C2 against Ricin. *Journal of Biological Chemistry*, **288**(35), 25165–25172.

[24] You, Z. et al. (2014) Preparation of egg yolk antibodies against BoNT/B and their passive protection in mouse models. *Human Vaccines & Immunotherapeutics*. **10**(8), 2321–2327.

[25] Hu, B. et al. (2011) Purification and Characterization of Gigantoxin-4, a New Actinoporin from the Sea Anemone *Stichodactyla Gigantea*. *International Journal of Biological Sciences*, **7**(6) 6, 729–739.

[26] For related research by other Chinese academic institutions see for example: Xu, X. et al. (2014) Proteomic analysis of the venom from the scorpion Mesobuthus martensii. *Journal of Proteomics*, **106**, 162–180; Gao, S. et al. (2021) *De novo* transcriptomic and proteomic analysis and potential toxin screening of *Mesobuthus martensii* samples from four different provinces. *Journal of Ethnopharmacology*, **265**, 113268.

described transcriptomic and proteomic analysis undertaken of the "toxin arsenal" of a species of Antarctic jellyfish,[27] a 2020 paper described transcriptomic and proteomic analysis and toxin screening of a novel Antarctic salp species,[28] and a 2021 paper described transcriptomic and proteomic analysis of the venom from the scorpioin *Mesobuthus martensii*.

The current authors have identified further separate lines of academic or medical investigation, with potential dual-use applicability that have been conducted by other Chinese institutions; indicative examples are detailed further. For example, a 2010 paper described how Chinese researchers created drosotoxin, a "chimeric toxin" from *Drosophila* antifungal defensin (drosomycin) and a scorpion sodium channel toxin, the novel toxin exhibiting potential analgesic properties in rats.[29] Further papers in 2011 and 2012 described the creation, functional characterisation, and investigation of the analgesic properties of drosotoxin analogues.[30]

A 2011 paper, involving scientists from the Laboratory of Pathogens and Biosecurity of the Beijing Institute of Microbiology and Epidemiology, stated that shiga toxin type 2 was a potential agent of bioterrorism and described investigations into the toxicokinetics of shiga toxin type 2 (a key virulence factor of shiga-producing *Escherichia coli*) following injection into rats.[31] A subsequent 2016 paper, again involving scientists from the Laboratory of Pathogens and Biosecurity of the Beijing Institute of Microbiology and Epidemiology, described screening and identification of

[27] Liang, H. et al. (2019) An integrated transcriptomic and proteomic analysis reveals toxin arsenal of a novel Antarctic jellyfish *Cyanea sp. Journal of Proteomics*, **208** 103483.

[28] Ye, R. et al. (2020) A combined analysis of transcriptomics and proteomics of a novel Antarctic *Salpa* sp. and its potential toxin screenings. *International Journal of Biological Macromolecules*, **160**, 1101–1113.

[29] Zhu, S. et al. (2010) Drosotoxin, a selective inhibitor of tetrodotoxin-resistant sodium channels, *Biochemical Pharmacology*, **80**, 1296–1302.

[30] Zhu, S. et al. (2011) DrTx (1–42), a C-terminally truncated analogue of drosotoxin, is a candidate of analgesic drugs. *Biochemical Pharmacology*. **81**(3), 425–431; Li, P. and Zhu, S. (2011) Molecular design of new sodium channel blockers. *Biochemical and Biophysical Research Communications*, **414**, 321–325; Li, P. and Zhu, S (2012) Mutational Analysis of the Analgesic Peptide DrTx(1–42) Revealing a Functional Role of the Amino-Terminal Turn. *PLoS One*, 7(2), e31830.

[31] Liu, Y-N. et al. (2011) Shiga toxin type 2 (Stx2), a potential agent of bioterrorism, has a short distribution and a long elimination half-life, and induces kidney and thymus lesions in rats. *Archives of Toxicology*, **85**, 133–140.

two peptide-based shiga toxin type 2 neutralisers with potential therapeutic value.[32] We also found work on *Shigella* involving scientists from the Fifth Medical Center of the Chinese People's Liberation Army (PLA), Beijing[33] and from the 309th Hospital of the PLA, Beijing.[34] Other papers, in 2008 and 2020 respectively, describe projects by the Third Military University on staphylococcal enterotoxins A, B, and C (SEA, SEB, SEC),[35] and the Third Military Medical University in Chongqing and the Army 954 Hospital of the Tibet Military Region on SEB.[36] Further work on SEB involved the 302 Hospital/5th Medical Center of the PLA General Hospital, and the Key State Laboratory of Pathogens and Biosecurity, both in Beijing.[37]

Scientists from the College of Pharmacy, Army Medical University, Chongqing, the Department of Pathology, Southwest Hospital, Army Medical University, Chongqing, and the Medical Corps Department, Unit 69016, PLA, Xinjiang, were part of a team that in 2021 reported the development of a 5-antigen *S. aureus* vaccine (rFSAV), which was under efficacy evaluation in a phase 2 clinical trial employing a mice model.[38]

Scientists from the Marine Biological Institute, College of Military Medicine, Second Military Medical University, Shanghai, and the Department of Laboratory Diagnosis, Changhai Hospital, Second Military

[32] Li, T. et al. (2016) A potential therapeutic peptide-based neutralizer that potently inhibits Shiga toxin 2 in vitro and in vivo. *Scientific Reports—Nature*, **6**:21837, DOI:10.1038/srep21837.

[33] Wang, X. et al. (2020) The *Shigella* Type III Secretion Effector IpaH4.5 Targets NLPR3 to Activate Inflammasome Signalling. *Frontiers in Cellular and Infection Microbiology*, **10**, 511708. Doi:10.3389/fcimb.2020.511708.

[34] Zheng, Z. et al. (2016) Bacterial E3 Ubiquitin Ligase IpaH4.5 of *Shingella flexneri* Targets TBK1 to Dampen Host Antibacterial Response. *The Journal of Immunology*, www.jimmunol.org/cgi/doi/10.4049/jimmunol.1501045.

[35] Wang, S. et al. (2008) A broad-spectrum inhibitory peptide against staphylococcal enterotoxin superantigen SEA, SEB, SEC. *Immunology Letters*, **121**, 167–172.

[36] Liu, Y. et al. (2020) Determining the immunological characteristics of a novel human monoclonal antibody developed against Staphylococcal enterotoxin B. *Human Vaccines and Immunotherapeutics*, **16**(7), 1708–1718.

[37] Liu, S. et al. (2019) Transcutaneous immunization of recombinant Staphylococcal enterotoxin B protein using a dissolving microneedle provides potent protection against lethal enterotoxin challenge. *Vaccine*, **37**, 3810–3819.

[38] Zeng, H. et al. (2021) An Immunodominant Epitope-Specific Monoclonal Antibody Cocktail Improves Survival in a Mouse Model of *Staphylococcus aureus* Bacteremia. *J.Infect Dis*, **233**(10), 1743–1752.

Medical University, Shanghai, reported work on paralytic shellfish poisoning (PSP) in 2016. They suggested that this was one of the top three global marine biological hazards, and that the most representative PST toxins are the closely related gonyautoxin 1/4 (GTX1/4), gonyautoxin 2/3 (GTX2/3), saxitoxin (STX), and neosaxitoxin (neoSTX). The paper reported on the successful development and use of aptamers (functional single-stranded DNA or RNA fragments screened from a random oligonucleotide library) for gonyautoxin 1/4, and concluded that[39]: "several other toxin aptamers such as STX, GTX2/3 and neoSTX will be obtained in the future and will be used as novel molecular recognition probes to construct a high-throughput and real-time … sensor for the detection of PSTs." This would seem to be a significant development, given the importance of saxitoxin in past concerns about toxins. It would clearly help in detecting and responding to such toxins, but it might also raise dual-use concerns in regard to the actual use of such toxins for hostile purposes including by facilitating the protection of the users.

Palytoxin (PTX) is much less well known than many other toxins, but it is another dangerous toxin, with illness reported from eating contaminated seafood. Scientists from the Department of Biochemistry and Molecular Biology of the College of Basic Medical, Second Military Medical University, Shanghai, and the Marine Biological Institute, College of Marine Military Medicine, reported in 2019 that[40]:

> In recent years we have been working on PTX research and successfully obtained a DNA aptamer named P-1852…which can bind with high affinity and specificity, and could serve as a molecular recognition element in diagnosis and biological activity inhibition assays for PTX.

In summary, it is clear that substantial dual-use research and associated activities are being undertaken by a wide range of Chinese institutions many of them controlled or linked to Chinese security or military forces. Whilst many of these activities are clearly intended for prophylactic or other medical or protective purposes, certain research may have less benign applications.

[39] Gao, S. et al. (2016) Gonyautoxin 1/4 aptamers with high-affinity and high-specificity: From efficient selection to aptasensor application. *Biosensors and Bioelectronics*, **79**, 938–944.

[40] Hu, B. et al. (2019) Study of the binding mechanism of aptamer to palytoxin by docking and molecular simulation. *Nature Scientific Reports*, **9**, 15494. https://doi.org/10.1038/s41598-019-52066-z.

3.3 China Brain Project

Over the past two decades, the technologies available to neuroscientists have developed rapidly and made it increasingly possible to understand the neuronal circuits in the central nervous system (CNS) that underly our behaviour, and the roles played by bioregulators in such processes. The obvious advantages of this work, for example, in helping people with brain dysfunctions and injuries have led States, including China, to initiate large-scale brain research projects over recent years. While the China Brain Project (CBP) is still a work in progress, it is clear that there will be two major research complexes of the project, one in Beijing in the North and one in Shanghai in the South of the county, and that these institutes would be linked to major research on the brain in other parts of the country.[41] Among the core partners in this project will be the Academy of Military Medical Sciences,[42] and scientists from military medical institutions and other defence-related facilities will be involved in much of the research.

Certain research strands of the CBP and the associated work of Chinese scientists on neurological systems and associated bioregulators (specifically signalling molecules) in a variety of simple animal models have potential dual-use applicability. For example, a Shanghai researcher in 2018 published on the operation of the *locus coeruleus* (LC, the "blue spot", the main brain site for noradrenaline production) during general anaesthesia in zebrafish.[43] A leading neuroscientist at Peking University in 2017 published on the role of a specific 5-hydroxytryptamine (5-HT) receptor in sleep homeostasis in *Drosophila*,[44] and another leading neuroscientist at the National Institute of Biological Sciences in 2017 published on the role of serotonin in the regulation of defensive behaviour in mice.[45] A researcher from the Institute of Neuroscience, State Key Laboratory of Neuroscience,

[41] For further analysis see: Dando, M. R. (2020) *Neuroscience and the Problem of Dual Use: Neuroethics in the New Brain Projects*. Springer Nature, Switzerland. (See Chapter 9: China's Brain Project, pp. 149–172).

[42] Cyrandski, D. (2018) Beijing launches pioneering neuroscience centre: large research facility will be key part of much-anticipated brain initiative. *Nature*, **356**, 157–158.

[43] Du, W-J. et al. (2018) The locus coeruleus modulates intravenous general anesthesia of zebrafish via a cooperative mechanism. *Cell Rep* **24**, 3146–3155

[44] Qian, Y. et al. (2017) Sleep homeostasis regulated by 5HT2b receptor in a small subset of neurons in the dorsal fan-shaped body of drosophila. *eLife*, **6**: e26519. https://doi.org/10.7554/eLife.26519.

[45] Lu, H. et al. (2017) A retinoraphe projection regulates serotonergic activity and looming-evoked defensive behaviour. *Nat Commun*, 8:14908.

Shanghai Institutes for Biological Sciences, Chinese Academies of Sciences, was a member of a multi-author team who in 2018 published on the role of orexin (hypocretin) neurons on wakefulness in mice.[46]

Because of the conservative nature of evolution, much of the significant work in neuroscience, including that in the State-level brain research projects, can be carried out in model organisms such as fruit flies, zebrafish, and rodents. However, the upper reaches of human brains are very different from those of other mammals, such as rodents, and therefore to understand our more complex behaviours and the mechanisms that produce them, work is being carried out on non-human primates (NHPs), like macaque monkeys. This has important dual-use implications because it is quite clear that previous biological weaponeers did not have the manipulation of basic functions of the brain as the sole objective of their work, but also sought to influence human emotions, cognition and consequent behaviour.[47]

This point is critical here as a particular focus of the CBP that could give rise to dual-use concerns relates to the investigations of the nervous system and behaviours of NHPs. As a group of commentators pointed out in 2017, this:

> raises concerns about tacit capabilities… and the yoking of NHP studies and findings to military agendas under programs of dual- or direct-use. The CAS [Chinese Academy of Sciences] and the Ministry of Science and Technology have supported dual-use and military research for the Chinese government, and a number of Chinese military medical centers are engaged in neuroscientific research, including the Fourth Military Medical University in Xi'an, the Third Military Medical University in Chongqing, and Southern Medical University (formerly First Military Medical University).

And these commentators went on to suggest that:

> Of particular note in such efforts is *Junweikejiwei,* the newly developed Chinese research agency that conjoins efforts of the CAS and China's Ministry of Defense, and which is modeled after the United States' Defense

[46] Ren, S. et al. (2018) The paraventricular thalamus is a critical thalamic area for wakefulness. *Science*, **362**, 428–434.

[47] See, for example, Dando, M. R. (2018) Advances in Understanding Targets in the Central Nervous System. Chapter 8, pp. 228–258 in Crowley, M. et al. (Eds.) *Preventing Chemical Weapons: Arms Control and Disarmament as the Science Converge*. Royal Society of Chemistry, London.

Table 3.1 Data showing monkey resources in China (2012 Statistics, China Experimental Monkey Breeding Association)

Breeding companies	40 (cynomolgus and rhesus monkeys)
Locations	Guangdong, Guanxi, Yuan, Hainan, Sichuan
Total number in colonies	Cynomolgus 250,000. Rhesus 40,000
Total production in 2012	Cynomolgus 60,000, rhesus, 10,000

From reference 142

> Advanced Research Projects Agency (DARPA), to engage rapid, high-risk/high-return approaches to bioscience and technology.[48]

It is certain that work within the CBP includes studies of higher functions of the brain using advanced biotechnology with NHP as test subjects.[49] For example, in a lecture in 2016[50] one of the leading Chinese researcher's slides gave an idea of the scale of the resources in China for research on monkeys (Table 3.1).

The lecture highlighted the "Goals of non-human primate research in China" which included *inter alia*: "1. Studies of the cognitive functions using non-human primate as the animal model" and "2. Generation of genetically modified monkeys as animal models of human brain disorders and for basic neurobiology research."[51] Another slide in the presentation was related to work showing that monkeys can be taught to pass one of the standard tests used to detect if animals are self-aware in the way humans are self-aware. The lecture also discussed the adaptation of the genetic manipulation technologies that were so crucial to the success of work on nervous systems in rodents, to work with monkeys' brains. The problem of the long period of time monkeys take to reach maturity was circumvented by growing their testes in nude mice so that they came to maturity and use in further genetic manipulations much faster. These

[48] Palchik G. et al. (2018) Monkey business? Development, influence, and ethics of potentially dual-use brain science on the world stage. Neuroethics, **11**, 111–114.

[49] Quin, Z. and Li, X. (2017) Non-Human primate models for brain diseases-towards genetic manipulations *via* innovative technology. *Neurosci Bull*, **33**(2), 238–250.

[50] Mu-ming Poo (2016) *China Brain Project and non-human primate research in China*. Presentation Number 25 at The Brain Forum, Lausanne. 27 May.

[51] Mu-ming Poo (2016) *China Brain Project and non-human primate research in China*. The Brain Forum, Lausannem slide 11.

studies are discussed in more detail in a study of the CBP as a whole.[52] In general it seems certain that in the coming decades such work will reveal much about the neuronal circuits underlying human behaviours, the roles played by bioregulators, and what goes wrong with those circuits when malfunctions occur.[53] Whilst the purported purposes of such research are benign, there are clear risks of malign application of such research including in the potential development of bioregulator weapons to grossly attack or subtly influence or subvert human cognition, feelings, and actions.

3.4 Central Nervous System–Acting Weapons

Concerns about potential malign application of the rapidly developing dual-use toxin and bioregulator research and parallel developments in neuroscience are exacerbated by evidence of China's development and production of law enforcement weapons employing unidentified CNS-acting chemicals (which have also been termed incapacitating chemical agents [ICAs]), from at least the mid-1990s onwards.[54] In 1995, marketing materials distributed internationally by the State-owned China North Industries Corporation (NORINCO) promoted the "BBQ-901: anaesthetic gun system". This weapon discharges a projectile, with an effective range of 40 metres, which on impact injects a liquid CNS-acting chemical into the target.[55]

In 1996, an entry on the BBQ-901 in *Janes Police and Security Equipment* reported that:

> Depending upon the particular anaesthetic specified, the victim will be rendered unconscious within 1 to 3 minutes, this time obviously varying with individuals and with the placement of the projectile. The effects wear off after 3 or 4 more minutes, giving sufficient time to place the victim in restraint.[56]

[52] Dando, M. R. (2020) *Neuroscience and the Problem of Dual Use: Neuroethics in the New Brain Projects.* Springer Nature, Cham, Switzerland. See Chapter 9, China's Brain Project, particularly, pp. 160–164.

[53] See for example on progress in understanding psychiatric illnesses, Deisseroth, K. (2021) *Connections: A Story of Human Feelings.* Penguin, London

[54] Crowley, M. and Dando, M. R. (2014) op. cit., pp. 14–20.

[55] China North Industries Corporation (NORINCO (Undated) *Security, Anti-Riot Weapons and Ammunition Brochure.* Undated, brochure distributed at MILIPOL security exhibition, Paris, 1995 (copy on file with the Omega Research Foundation), p. 11.

[56] Hogg, I. (Ed.) (1996) *Janes Police and Security Equipment 1995–1996.* Janes Information Group Limited, Coulsden, Surrey. p. 306. An essentially identical listing appeared in subsequent editions, with the last being: McBride, M. (Ed.) (2006) *Janes Police and Security Equipment 2005–2006.* Janes Information Group Limited, Coulsden, Surrey, 2006, p. 518.

According to NORINCO:

> The Model BBQ-901 Anaesthetic system is a fine unlethal [sic] special weapon system for SWAT units and other special usage…. It can be used for reconnaissance and capture of criminals in a concealed place. It is also used as a riot control weapon to subdue the ruffians and maintain public order.[57]

In 2004, essentially similar if not identical, the "BBQ-901 narcosis gun" was promoted by a second Chinese State-owned company, State 9616 Plant, at the Asia Pacific China Police Expo held in Beijing.[58] The narcosis gun was subsequently promoted by State 9616 Plant at the 2006 Asia Pacific China Police Expo as shown in Fig. 3.1.[59]

In March 2012, *Defence Asia Review* reported that a "recent public display" by the Hong Kong garrison of the People's Liberation Army (PLA) included "a BBQ-901 tranquiliser gun (a pistol type air gun fitted with a folding stock)".[60] The author of this article had in 2011 photographed a previous display of the BBQ-901 by the PLA in Hong Kong as shown in Fig. 3.2.[61] As of 6 June 2022, there is no further information publicly available regarding the stockpiling or employment of this weapon within China, nor of international transfers.

Although NORINCO describe the BBQ-901 as an "anaesthetic gun system", the specific CNS-acting agent or agents originally developed and utilised have not been named by the manufacturer, or identified by independent analysis. Consequently, it is not possible to determine whether this system as originally developed employed pharmaceutical chemicals,

[57] NORINCO brochure (undated) op. cit. p. 11.

[58] State 9619 Plant (Undated) *Company Brochure*. Distributed at Asia Pacific China Police Expo 2004, 23rd–26th June 2004, Beijing Exhibition Centre, Beijing, China, (copy on file with the Omega Research Foundation).

[59] An apparently identical *State 9616 Plant Company Brochure* was distributed by company representatives at Asia Pacific China Police Expo 2006, 24th–27th May 2006, Beijing Exhibition Centre, Beijing, China. (Copy of brochure on file with the Omega Research Foundation). For further information about State 9619 Plant products including the BBQ-901 see full exhibitors list: http://www.cpexhibition.com/police/police_main.html#2006expo (accessed 25th March 2014

[60] Arthur, G. (2012) New Equipment in Hong Kong, *Defence Review Asia*, 19th, http://www.defencereviewasia.com/Articles/153/NEW-EQUIPMENT-IN-HONG-KONG (accessed 11th August 2014), p. 35.

[61] Email correspondence to Dr M. Crowley, BNWLRP, from Mr G. Arthur, 16th August 2014.

Fig. 3.1 Poster for "BBQ-901 Narcosis Gun" on Display on State 9616 Plant Stand at Asia Pacific China Police Expo 2006, Beijing, China, 24–27 May 2006. Copyright: Robin Ballantyne/Omega Research Foundation.

toxins, or bioregulators. Similarly, it is unclear whether the BBQ-901 could be used as a delivery mechanism for a wider range of CNS-acting agents and whether such agents have been developed.

Whilst the weaponisation of any toxic chemical (including toxins and bioregulators) is prohibited by the CWC, it was long contested whether this prohibition also applied to law enforcement use of certain CNS-acting chemicals. On 1 December 2021, the 26th Conference of States Parties to the CWC adopted a landmark Decision to effectively outlaw the aerosolised use of CNS-acting chemical agents for law enforcement

Fig. 3.2 "BBQ-901 Tranquiliser Gun" being displayed at a People's Liberation Army 'Open Day', Shek Kong Air Base, Hong Kong, 2 May 2011. Copyright: Gordon Arthur/King Arthur's Writes.

purposes.[62] Although 85 countries supported the Decision, China was among ten States that voted against it. It is currently unclear whether China will accept this Decision and will implement it fully, including with regard to aerosolised bioregulator or toxin CNS weapons. Unfortunately, the Decision only prohibited law enforcement use of *aerosolised* CNS-acting chemicals, so the legitimacy of China's "narcosis gun" is still contested.

[62] CWC (2021) *Decision: Understanding regarding the aersolised use of central nervous system-acting-chemicals for law enforcement purposes.* C-26/DEC.10. Conference of States Parties, 26th Session. Organisation for the Prohibition of Chemical Weapons, The Hague.

3.5 Research and Development of Riot Control Agent Delivery Mechanisms

Chinese companies have researched and developed a range of law enforcement RCA means of delivery—including hand-held sprayers which disseminate oleoresin capsicum (OC)—a sensory irritant of biological origin, in limited quantities and over relatively small areas. They are promoted for use by Chinese law enforcement agencies and also for export.[63] If employed in appropriate amounts and circumstances, they would appear to be consistent with the BTWC and CWC.[64]

In contrast, Bradford University and the Omega Research Foundation identified the development by Chinese companies and State entities of a range of 'wide area' RCA means of delivery of potential concern that could disseminate these agents over large areas or extended distances. They included large backpack or tank spray devices, vehicle-mounted RCA dry spray devices, multi-barrel launchers and associated RCA projectiles, automatic grenade launchers and associated RCA grenades, RCA mortar projectiles and other large calibre projectiles, and RCA area denial munitions and unmanned aerial vehicles capable of RCA dispersal.[65] In the majority of cases, the Chinese manufacturers did not identify the specific RCA employed, but instead described the chemical agent as a "tear gas"; if an RCA was identified, it was normally CS. Many of these delivery mechanisms appear capable of employing a range of RCAs, and a

[63] For examples of 'limited area' law enforcement OC sprayers manufactured or promoted by Chinese companies, see https://m.made-in-china.com/hot-china-products/Oleoresin_Capsicum_Spray.html. See also: Amnesty International and the Omega Research Foundation (2014) *China's Trade in Tools of Torture and Repression*. ASA 17/042/2014.

[64] There have been reports of excessive or inappropriate use of 'limited area' OC means of delivery by Chinese law enforcement officials. Such practice would appear to contravene relevant human rights law and standards. See for example: Amnesty International (2019) *How not to police a protest: unlawful use of force by Hong Kong police*. ASA 17/0576/2019; Amnesty International and the Omega Research Foundation (2014) op. cit.

[65] Crowley, M. (2015) *Chinese 'wide area' riot control agent means of delivery: implications for the Chemical Weapons Convention*. University of Bradford/Omega Research Foundation, November; See also: Crowley, M.(2013) *Drawing the line: regulation of 'wide area' riot control agent delivery mechanisms under the Chemical Weapons Convention*. University of Bradford/Omega Research Foundation, April; and Crowley, M. (2015) *Tear gassing by remote control: The development and promotion of remotely operated means of delivering or dispersing riot control agents*. University of Bradford/Omega Research Foundation/Remote Control Project, December.

number potentially could deliver, or be adapted to deliver, OC and its synthetic analogues.

In 2018, the Hong Kong police acquired three, reportedly German-manufactured, water cannon.[66] These vehicles each contained two water spray devices capable of employing large quantities of water that can be mixed with an RCA and/or a dye (to identify protestors for subsequent arrest), and can target individuals or crowds, up to 50 metres away.[67] Amnesty International stated that "The use of water cannons with irritants [RCAs] and dye in compact residential areas poses a threat to freedom of expression and peaceful assembly." They also expressed concern that it would be "impossible to deliver an appropriate, targeted dose of the irritant [RCA]".[68] From August 2019, there were repeated reports of Hong Kong police employing water cannon firing water mixed with blue dye and/or the RCA against both violent and non-violent protestors, in disputed circumstances.[69] Following concerns raised by the environmental NGO Greenpeace, the Hong Kong police reportedly stated that the blue dye was "harmless" and confirmed that the RCA employed was PAVA (pelargonic acid vanillylamide, a synthetic capsaicinoid) which they stated

[66] Cheng, K. Hong Kong police to receive 3 water cannon vehicles, worth HK$27m, this year, Hong Kong Free Press, 19 January 2018, updated 31 March 2020, https://hongkongfp.com/2018/01/19/hong-kong-police-receive-3-water-cannon-vehicles-worth-hk27m-year/; Oltermann, P. Hong Kong activist to Germany: stop selling riot control kit to city, 11 September 2019, https://www.theguardian.com/world/2019/sep/11/hong-kong-activist-to-germany-stop-selling-riot-control-kit-to-city.

[67] Cops buy three more water cannon trucks at HK$9.9 million, The Standard (Hong Kong), 22 December 2021, https://www.thestandard.com.hk/breaking-news/section/4/184952/Cops-buy-three-more-water-cannon-trucks-at-HK$9.9-million.

[68] Hong Kong: Water cannons pose real danger in hands of trigger-happy police, Amnesty International, 10 August 2019, https://www.amnesty.org/en/latest/news/2019/08/hong-kong-police-water-cannon-danger/.

[69] For media coverage see for example: Creery, J. Hong Kong police water cannon truck fires blue-coloured water as protesters besiege gov't HQ, Hong Kong Free Press, 31 August 2019 updated 31 March 2020, https://hongkongfp.com/2019/08/31/breaking-police-water-cannon-truck-fires-blue-coloured-water-hong-kong-protesters-besiege-govt-hq/; Hong Kong: Blue-dyed water fired at protesters defying ban, BBC, 31 August 2019, https://www.bbc.co.uk/news/av/world-asia-49536000; Hong Kong protests: police fire water cannon with blue dye as crowds defy ban, Agence France-Presse/The Guardian, 21 October 2019, https://www.theguardian.com/world/2019/oct/21/hong-kong-protests-police-fire-water-cannon-with-blue-dye-as-crowds-defy-ban;

would cause only temporary discomfort.[70] In December 2021, the Hong Kong newspaper, *The Standard*, reported that Hong Kong police had acquired three additional water cannon trucks, manufactured in China. Although smaller, they were similar to the previous vehicles and were capable of spraying water mixed with PAVA.[71] There is no publicly available information concerning the maximum concentration nor total amounts of active PAVA that can be delivered from either the Chinese or German water cannon.

3.6 CWC Article X Declarations and the BTWC Confidence-Building Measures

Under both the BTWC and the CWC, States Parties are permitted to conduct research and associated activities, including the production of appropriate quantities of potential weapons agents for "prophylactic, protection and other purposes" under the BTWC, and for "protective purposes" under the CWC. Recognising the danger that such activities could mask weapons programmes, both the OPCW and the BTWC States Parties have introduced relevant reporting and transparency mechanisms.

Consequently CWC States Parties are required under Article X of the Convention to provide annual declarations to the OPCW Technical Secretariat on "national programmes related to protective purposes". There is currently no requirement to make Article X declarations public, and China has not done so.[72] However, in its response to the authors' information request, the Chinese Permanent Mission to the OPCW stated that "All the activities for protective purposes carried out by China are consistent with the provisions of the CWC and are subject to verification and supervision of the OPCW …. Regarding the States Parties' obligation under Paragraph 4 of Article X, China has submitted information on its national programme for protection against chemical weapons since 2012."[73]

Similarly, to enhance transparency, BTWC States Parties agreed to submit annual confidence-building measure (CBM) reports from 1987 to the

[70] Chan, H. Greenpeace questions Hong Kong police claim that blue dye from water cannon is 'harmless', Hong Kong Free Press, 25 October 2019, updated 31 March 2020. https://hongkongfp.com/2019/10/25/greenpeace-questions-hong-kong-police-claim-blue-dye-water-cannon-harmless/.

[71] The Standard (Hong Kong) (22 December 2021) op.cit.

[72] OPCW, *CWC* (1993) op. cit. Article X, paragraph 4.

[73] Qian Wang (2021 op. cit.

States Parties/ISU on relevant national activities. In their response to the authors, the Chinese Geneva Mission to the UN highlighted that "In accordance with the decision adopted by the Second Review Conference of the BWC, since 1988, China has submitted its confidence-building measures in a timely manner."[74] According to the UNOG/ISU database, China has submitted CBM reports to the BTWC States Parties/ISU on an annual basis, with the latest CBM submitted in 2022. However, none of these CBMs are publicly available.[75]

Consequently, it is not possible for civil society to directly establish whether China has reported to either the OPCW or BTWC States Parties/ISU on toxin and bioregulator research and other related activities undertaken or facilitated by defence establishments, and if so, whether it has identified them as being for protective or other permitted purposes. Some information however can be obtained from the reports of other States and from civil society.

The US, which like all BTWC States does have access to such reports, has repeatedly raised concerns about China's BTWC CBM reporting, particularly with regard to its failure to declare reported former biological weapons production facilities. For example in its 2005 *Arms Control Compliance Report*, the US State Department "assessed that the information submitted therein continues to be inaccurate and misleading." It further noted that "BWC CBMs since 1991 have called on the States Parties to declare, among other things, their past offensive activities, which China has not done. On the contrary, China insists it never had such a program at all."[76] In its 2010 *Arms Control Compliance Report*, the US State Department assessed that "the voluntary BWC CBM declarations China has submitted have neither documented the offensive BW program it possessed prior to its accession to the BWC in 1984, nor documented that China has eliminated the program or any remaining biological munitions in accordance with the BWC."[77] In its 2022 *Arms Control Compliance Report*, the US State Department noted that although China has submitted BWC CBMs each year since 1989, "the PRC's CBM reporting has never declared these [reported biological

[74] Disarmament team (2021) op. cit.

[75] United Nations, Confidence Building Measures, China, https://bwc-ecbm.unog.ch/state/china (accessed 24 April 2022).

[76] United States, (2005) *Compliance Report—Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* Department of State, August, p. 21.

[77] United States (2010) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* Department of State, July, p. 18.

weapons production] facilities or otherwise disclosed it ever pursued an offensive BW program, and the PRC has never acknowledged publicly or in diplomatic channels its past offensive program."[78] As noted previously, in correspondence to the authors, the Chinese government forcefully asserts that "China has all along implemented its obligations under the BWC…in a comprehensive and earnest manner"[79] rejects allegations made to the contrary by the US government.[80]

3.7 Concluding Remarks

Certain States and commentators have asserted that China previously had a biological and toxin weapons programme which it has not declared and which they claim may not have been fully dismantled. China strongly rejects these accusations. It should also be acknowledged that although there have been historical reports of limited biological weapon development activities, there appears to be no evidence of any Chinese use of toxin or other biological and chemical weapons during any of the armed conflicts that China was involved in.

Open-source information indicates a range of contemporary toxin and bioregulator research, of possible dual-use applicability, has been carried out by Chinese military and military-related institutions and researchers. Whilst certain such research has clear medical or protective applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied. China has submitted relevant reports to the OPCW and the ISU/BTWC States Parties, which potentially cover toxin and bioregulator dual-use research and associated activities. However, the substance of such reports does not appear to have convinced at least one State of its good intentions, notably with regard to previous reported biological weapons production. Civil society does not have access to these reports as China has not published them in the open literature. In combination then these indicators suggest that there remains considerable distrust, in certain quarters, about China's dual-use toxin and bioregulator research activities.

[78] United States *Arms Control Compliance Report* (2022) op. cit. p. 35.
[79] Permanent Mission of China to the UN in Geneva, Disarmament team (2021) op. cit.
[80] Qian Wang (2021) op. cit.

It would be beneficial if China specifically addressed concerns about its previous and contemporary dual-use toxin and bioregulator research and associated activities through the BTWC CBM annual reporting process and through its annual CWC Article X declaration. Furthermore, to increase public confidence in this area, it would be beneficial if China published unredacted version of such reports.

Chinese State companies have developed and produced CNS-acting weapons for use against individuals and such weapons have been documented in the possession of the PLA. In December 2021 China voted against the Decision adopted by CSP 26 prohibiting law enforcement use of aerosolised CNS-acting chemicals. It would be beneficial if China clarified whether it now accepted this Decision and would implement it fully, including with regard to aerosolised bioregulator or toxin CNS weapons.

Chinese companies have developed a range of 'wide area' RCA means of delivery. A number of these are potentially capable of disseminating, or being adapted to disseminate, OC (a sensory irritant of biological origin) or PAVA (a synthetic analogue) over large areas or extended distances. China should provide details of which, if any, Chinese military, security or police forces possess stocks of these means of delivery, and if so provide details of the nature of such stockpiles; and the circumstances under which such means of delivery would be employed.

Those States concerned about China's previous and contemporary dual-use toxin and bioregulator research and associated activities should employ the relevant consultation and/or investigation and fact-finding mechanisms under the CWC and BTWC, as appropriate, to raise and resolve their concerns.

CHAPTER 4

The India Case Study

4.1 Introduction

India signed the Geneva Protocol in 1925, ratified the Biological and Toxin Weapons Convention (BTWC) in 1974, and the Chemical Weapons Convention (CWC) in 1997. To date, there is no evidence that India has developed, acquired, stockpiled, or utilised toxin or bioregulator-based weapons specifically intended for armed conflict. This chapter will explore areas of potential concern regarding India's dual-use research and associated activities relating to toxins and other substances of biological origin, or their analogues. Firstly, the chapter will examine development or acquisition by defence and law enforcement bodies of certain 'wide area' riot control agent (RCA) means of delivery capable of disseminating RCAs—potentially including oleoresin capsicum (OC), a sensory irritant of biological origin, and pelargonic acid vanillylamide (PAVA), a synthetic capsaicinoid—over wide areas or extended distances. The chapter will also explore research by Indian scientists into a range of malodorants apparently with the intention of developing them for use in law enforcement crowd dispersal operations; and also research into certain pharmaceutical chemicals that could have dual-use application in relation to ICA/CNS-acting agents. Finally the chapter will then more extensively examine recent

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research conducted by Indian military-related and funded institutions and scientists into toxins and other substances derived from a broad range of indigenous Indian stinging and other poisonous plants.

4.2 Research and Development of Riot Control Agent Means of Delivery

A number of Indian State defence and law enforcement bodies have researched, developed, manufactured and/or marketed a range of 'limited area' RCA means of delivery, including those disseminating small quantities of OC, a sensory irritant of biological origin, in relatively narrow areas. A key organisation has been the Tear Smoke Unit (TSU), established in 1976 by the Indian Ministry of Home Affairs to undertake research and development of indigenous "less than lethal munitions" principally for the Indian police and armed forces "to deal with various law and order and peace time operational situations", and additionally for export. The TSU has subsequently developed at least 46 RCA munitions and other means of dispersal.[1] These include projectiles employing sensory irritants of biological origin, notably the weapons-launched 38mm Stun Lac (Chilli) shell and 38 mm Soft Nose-LR (Long Range) (OC) shell; the hand-thrown Stun Lac (Chilli) grenade, and the hand-thrown or weapons-launched tear smoke grenade (OC).[2] Additional relevant research has been undertaken in further Indian defence organisations, with, for example, scientists at the Defence Research Laboratory (DRL) and the Defence Research and Development Organisation (DRDO) exploring the effects of OC notably on mammalian eyes.[3] There have also been reports that the DRDO has developed a range of 'limited area' OC delivery devices—including hand-thrown "chilli" grenades—for use by Indian police and military forces.[4] From the information available, and given the limited quantities of OC disseminated by the TSU and DRDO projectiles, their use by law enforcement officials in

[1] For further information concerning organisation and product range see the Tear Smoke Unit website, http://www.tearsmoke.org/index.htm (accessed 20 January 2022).

[2] Tear Smoke Unit, *Some products*. Available at http://www.tearsmoke.org/index.htm (accessed 20 January 2022).

[3] Krishnatreyya, H. et al (2018) Capsaicin, the primary constituent of pepper sprays and its pharmacological effects on mammalian ocular tissues. *European Journal of Pharmacology*, **819**, 114–121.

[4] Bhaumik, S. (2010) India scientists hail 'multi-purpose' chillis, *BBC News*, 24 March; Singh, R. (2016) Army backs pepper shots, chilli grenades over pellet guns in Kashmir. *Hindustan Times*, 15 August; Dixit, R. (2020) DRDO develops 'mirchi bomb' inspired from the spicy bhut jolokia, *The Week*, 9 January.

appropriate numbers and circumstances would appear to be consistent with the BTWC and CWC.[5]

In addition, certain Indian defence and law enforcement bodies have developed or acquired means of delivery that are capable of disseminating large quantities of RCAs (potentially including OC or PAVA) over greater distances or wider areas. In a 2018 article highlighting "military and civil applications" of "DRDO herbal technologies", a DRDO author discussed DRDO development of OC products for use in law enforcement and low intensity conflicts. The author highlighted potential delivery mechanisms for OC (and by extension, PAVA) stating that "[C]apsi-based products can be used as a handheld spray or as a hand grenade or thrown through projectile/launchers as ball or shell or *through water cannon as fine spray*" (emphasis added).[6] Given the listing of water cannon as a potential means of OC (or PAVA) delivery, it is notable that DRDO has developed the Varun-Vehicle Mounted Water Cannon System intended to provide "an effective, non-lethal means for dispersal of violent mobs". The system which has a capacity to hold 12,000 litres of water can "deliver continuous / pulsating water jet through two rotatable platform cannons mounted on the top of the vehicle…[and]…*provision to mix irritant /* indelible ink has also been incorporated in the cannon system" (emphasis added). According to DRDO more than 84 units have been produced and are being used by police forces throughout the country.[7] No information has been provided identifying the "irritant" or "irritants" that can be employed in this system.

The TSU developed and currently promotes the Agni Varsha, a 38 mm multi-barrel launcher that can fire seven tear smoke shells singly or

[5] However, there have been unconfirmed reports of excessive or inappropriate use of 'limited area' OC means of delivery by Indian law enforcement officials. If confirmed, such practice would appear to contravene relevant human rights law and standards. See for example: Kashmir Watch (2013) *Stop using pepper gas in Kashmir: Amnesty to Govt*. 21 March. Available at http://kashmirwatch.com/stop-using-pepper-gas-in-kashmir-amnesty-to-govt/; Global Press Journal (2013) *Kashmiri Community Links Police Use of Pepper Gas on Protesters to Civilian Deaths*, April. Available at https://globalpressjournal.com/asia/indian-administered_jammu_and_kashmir/kashmiri-community-links-police-use-ofpepper-gas-on-protesters-to-civilian-deaths/136; Kashmir Life (2017) *Pepper Paradise*. March. Available at https://kashmirlife.net/pepper-paradise-issue-no-49-vol-08-134390/.; Kashmir Reader (2018) *SHRC gives police one week to submit SOP on use of pepper gas.* July. Available at https://kashmirreader.com/2018/07/18/shrc-gives-police-one-week-to-submit-sop-on-use-of-pepper-gas/.

[6] Arora, R. (2018) *Herbal Technologies: Military and Civil Applications.* DRDO, 18 April.

[7] DRDO (undated) *Water cannon*. Available at https://www.drdo.gov.in/water-cannon.

simultaneously and can be used either from ground level or by fitting on a vehicle. It has a range of 90–135 metres and can blanket an area of approximately 100 metres × 60 metres in a seven-launch salvo, which the TSU has claimed make the launcher effective for covering large areas".[8] According to the TSU, the Agni Varsha can be used for: "dispersal of violent mobs; …flushing out terrorists from fields/dense jungles/broken ground;" and in the "conduct of vehicle mounted operations".[9] The Agni Varsha is designed to employ a variety of compatible projectiles developed by the TSU, including a 38 mm tear smoke shell containing CS. Although the launcher appears potentially capable of delivering other RCAs, possibly including OC and PAVA, no such compatible projectiles have been promoted on the TSU website, to date. A second Indian entity, the Central Workshop and Store, Border Security Force, Tekanpur (CENWOSTO), also promotes (and apparently manufactures) the Agni Varsha. In addition to the standard seven-barrel version, CENWOSTO promotes (and apparently manufactures) a nine barrel modified Agni Varsha and a 15 barrel version called the Agniprahar. All CENWOSTO launcher versions appear capable of firing "tear smoke" shells.[10]

According to an 8 April 2015 *Agence France-Presse* (*AFP)* report, police in the city of Lucknow, in the northern Indian State of Uttar Pradesh, acquired five unmanned aerial vehicles (UAVs) incorporating a "pepper spray" delivery mechanism.[11] The UAVs could each reportedly carry two kilograms of unspecified "pepper spray" and could be flown within a one kilometre radius of their operator. Each UAV was also equipped with a high-resolution camera. Although there was no further

[8] Tear Smoke Unit (undated) *Border Security Force Tekanpur Multi Barrel launcher Agni Varsha product brochure*. Gwalior, India.

[9] Ibid.

[10] For details of the Multi-barrel launcher (MBL) "Agnivarsha", Modified MBL "Agnivarsha", and the Agniprahar MBL, see Central Workshop and Stores, Border Security Force, Tekanpur, Products, available at https://cenwosto.org/ShowPageContant/66/Products (accessed 5 June 2022).

[11] AFP (2015) *Indian police to use pepper-spraying drones on unruly protesters*. 7th April. This was subsequently reprinted very widely. See for example: Indian police to use 'pepper-spray drones' on protesters, *Daily Telegraph*, 8th April 2015. Available at http://www.telegraph.co.uk/news/worldnews/asia/india/11521639/Indian-police-to-use-pepper-spraydrones-on-protesters.html. (Accessed 18th November 2015); Pepper spraying drones could be used on unruly crowds by Indian police, *The Guardian*, 8th April 2015 Available at http://www.theguardian.com/world/2015/apr/08/pepper-spraying-drones-could-be-used-on-unruly-crowds-byindian-police. (Accessed 18th November 2015).

information concerning the make or manufacturer of the UAVs, each was reported to have cost 600,000 rupees (£6400).[12] In an interview with *AFP*, the police chief of Lucknow, Mr Yashasvi Yadav, stated that Lucknow police had successfully test-flown the UAVs which he explained were intended for use in crowd-control situations. According to Mr Yadav, "[T]he results were brilliant. We have managed to work out how to use it to precisely target the mob in winds and congested areas…. Pepper is non-lethal but very effective in mob control. We can spray from different heights to have maximum results."[13] Although the UAVs were reportedly intended to be introduced in April 2015,[14] to date there have been no reports of their subsequent employment by Lucknow police or by other Indian police forces.

4.3 Malodorants

Although there have been no reports of the use of malodorant weapons by Indian military or police forces, there are indications that such entities have explored acquisition of these weapons, and that Indian scientists, including those associated with the DRDO, have undertaken research potentially related to malodorant weapons development. In 2009, DRDO scientists submitted an Indian patent application for a "negative fragrance formulation" which was "non toxic in nature, chemically stable and efficient and is used to deter and drive away anti-social elements from a particular place."[15] The formulation "…can be sprayed to repel/annoy any crowd to disburse from that area by its obnoxious odor without killing them."[16] According to the patent application the "[p]referred compounds suitable for use in the formulation of this invention include alkyl thiazole, furfuryl mercaptan and the formulation may include dl-menthol and a diluent."[17] Although the patent was granted on 29 August 2014, there is no indication whether DRDO scientists have undertaken further research and/or development of this malodorant.

[12] Ibid.
[13] Ibid.
[14] Ibid.
[15] Indian patent application number 2053/DEL/2009, patent number 262598, patentee: Director General, DRDO; publication date: 5 September 2014, grant date: 29 August 2014.
[16] Ibid.
[17] Ibid.

In July 2017 the *Hindustan Times* and subsequently other Indian and Israeli media sources reported that the Central Reserve Police Force (CRPF) had assessed the Israeli-developed Skunk malodorant weapon[18] for potential use for crowd control in Kashmir and elsewhere in India.[19] The CRPF reportedly tested the Skunk in Delhi "on a captive crowd… consisting of CRPF personnel and general public."[20] However it proved to be ineffective and was not purchased. According to an official engaged in the test, the crowd "managed to tolerate the smell without much difficulty. Maybe Indians have a higher threshold of tolerating stench,"[21] Also in July 2017, several Indian media sources reported that scientists at the Fragrance and Flavour Development Centre (FFDC), a commercial perfume manufacturer based in Kannauj, Uttar Pradesh, had developed a malodorant.[22] According to the FFDC principal director: "The odour producing chemicals would be put in a small glass capsule. These capsules will be fired through tear guns…[the capsule]… will burst and create smoke having unbearable odour".[23] Although no timescale was given, the malodorant was reportedly due to be assessed by the DRDO and if approved it could then potentially be employed by the Indian Army, apparently for crowd control activities. No further information has been made public.

[18] The Israeli manufacturer has claimed that though Skunk is a pungent foul smelling liquid that is highly effective at dispersing crowds, it is non-toxic. Since 2008, Israeli security forces have used Skunk spray devices or water cannon, commonly against Palestinian demonstrators, often in disputed circumstances. For further discussion see: Crowley, M. (2016) op. cit. pp. 45–46 & 71–72.

[19] Ahuja, R. Smelly bomb planned to douse protests doesn't raise a stink, *Hindustan Times*, 27 July 2017; Israeli-made Sewage-stinking Weapon Not Smelly Enough to Deter Indian Protesters, *Haaretz*, 31 July 2017; Surkes, S., Indians unfazed by Israeli-made stink bomb, *Times of Israel*, 30 July 2017.

[20] Ahuja, R. (2017) op. cit.

[21] Ibid.

[22] Ahmad, Q., Indian Army May Use 'Stink Bomb' to Control Stone-pelters in Kashmir, *News18.com*, 7 July 2017; Makers of India's most famous perfume develop stink bomb, *Hindustan Times*, 6 July 2017; Kannauj Perfumers Develop Stink Bombs To Counter Stone-Pelters In Kashmir, *Indiatimes*, 8 July 2017.

[23] Makers of India's most famous perfume develop stink bomb, *Hindustan Times*, 6 July 2017.

In a 2021 paper,[24] DRL/DRDO researchers describe the design and initial assessment of a "nonlethal riot control combinational formulation (NCF)", an oil and water emulsion containing 1.5% oleoresin capsicum combined with the malodorant skatole (3-methylindole), "a tryptophan metabolite having a fecal odor, [that] has been chosen for triggering the threat of ill health that might cause vomiting, dizziness, fatigue, etc."[25] The formulation also contains an unidentified colour dye intended for marking those targeted. According to the DRL/DRDO researchers, the NCF "has been designed in such a way that [it] can be incorporated and easily delivered through various conventional technologies such as water cannon, impact projectiles, high-pressure hoses to disperse unruly groups of individuals like crowds, rioters etc., with the intended delivery of NCF in a continuous or intermittent stream instead of a stream of high-pressure water."[26] Following the application of the NCF to animal models (Wistar rats) through acute inhalation exposure, various respiratory parameters were examined.[27] The researchers reported that "…exaggerated physiological change like sensory irritation, changes in lung functional variables, increased pro-inflammatory cytokines, etc. were noticed initially without airway obstruction…no abnormality was found in lung tissue architecture." The researchers concluded that "this formulation can be explored as a nonlethal riot control agent intending to generate discomfort but with early reversibility of sensory irritation and no recurrence of toxicity."[28] The DRL/DRDO scientists highlighted that further research was needed "…uncovering the underlying role of the formulation in other exposed tissues and a better understanding in the molecular, genomic, receptor level, and [that] clinical trials will envisage the consequences of the broad range of vulnerability if any."[29] There is no indication of whether any of these further research activities have been undertaken to date.

[24] Das, S., et al. (2021) Assessment of toxicological consequences upon acute inhalation exposure to chemically improvised nonlethal riot control combinational formulation (NCF) containing oleoresin capsicum and skatole, Toxicology Research, volume 10, pp. 1129–1143, 27 October.

[25] Das, S. et al. (2021) op. cit. p. 130.

[26] Das, S. et al. (2021) op. cit. p. 130.

[27] Das, S. et al. (2021) op. cit. p. 129.

[28] Das, S. et al. (2021) op. cit. p. 129.

[29] Das, S. et al. (2021) op. cit. p. 141.

4.4 Incapacitating Chemical Agents/CNS-Acting Chemical Agents

The current authors could find no indications of contemporary toxin or bioregulator research associated with incapacitating chemical agents (ICA)/CNS-acting chemicals, by scientists at Indian defence establishments. However, scientists at DRDO have previously conducted dual use research into pharmaceutical chemicals that could be employed as such agents. This has included work related to the synthesis, aerosolization and bio-efficacy of fentanyl and its analogues, as described in papers from 2005 till 2018.[30] In 2014, the Indian CWC National Authority gave "categorical and unambiguous clarifications" that India has no stockpile of ICAs/CNS-acting chemicals, is not involved in the weaponization of ICAs/CNS-acting chemicals and that "research on fentanyl is being carried out in India only for the purpose of protection."[31] It is not known whether such activities have been reported to the OPCW as part of India's annual declaration of national programmes related to "protective purposes". On 1 December 2021, the 26th Conference of States Parties to the CWC [CSP-26] adopted a Decision to effectively outlaw the aerosolized use of CNS-acting chemical agents for law enforcement purposes.[32] Although 85 countries supported the Decision, India was among 33 States that abstained. It is currently unclear how India will implement the CSP-26 Decision, including with regard to aerosolized bioregulator or toxin CNS weapons.

[30] See Crowley, M. and Dando, M. (2014) op. cit. pp. 34–38 for details of papers published from 2005 to 2014. In addition see: Yadav, S., et al. (2018) Biochemical, Oxidative, and Physiological Changes Caused by Acute Exposure of Fentanyl and Its 3 Analogs in Rodents, International Journal of Toxicology, volume 37, number 1, pp. 28–37; Yadav, S. and Bhattacharya, R. (2018) Acute Immunomodulatory Effects of Fentanyl and its Three New Analogues in Swiss Albino Mice Defence Life Science Journal, volume 3, number 1, January 2018, pp. 24–30.

[31] Correspondence to Dr M. Crowley BNLWRP, from Dr P. Trivedi, Secretary (Performance Management) Government of India and Chairman, Indian National Authority for the Chemical Weapons Convention, 7th August 2014, cited in Crowley, M. and Dando, M. (2014) op. cit. p. 47.

[32] CWC (2021) *Decision: Understanding regarding the aerosolised use of central nervous system-acting-chemicals for law enforcement purposes.* C-26/DEC.10. Conference of States Parties, 26th Session. Organisation for the Prohibition of Chemical Weapons, The Hague.

4.5 Contemporary Dual-Use Toxin Research Into "Novel Bio-Threat Agents"

According to its website, the Defence Research and Development Organisation (DRDO) is the "[R] and D wing of [the Indian] Ministry of Defence, with a vision to empower India with cutting-edge defence technologies and a mission to achieve self-reliance in critical defence technologies and systems." It is comprised of "*a network of more than 50 laboratories which are deeply engaged in developing defence technologies covering various disciplines, like …armaments…advanced computing and simulation…life sciences…and agriculture*".[33]

It is a simple matter to find publications in the open literature by Indian scientists working for the DRDO that deal with toxins in the manner that would be expected from scientists undertaking research for legitimate defensive purposes such as the development or improvement of detection, prophylactic or other countermeasures. Such papers were produced, for example, on botulinum toxin,[34] ricin,[35] and abrin.[36] However, our review of publicly available scientific papers indicates that researchers at or associated with the DRDO have also undertaken research to discover, identify and assess native plants that could be employed as "novel bio-threat agents", isolate the toxins they produce and examine their characteristics. The purpose or purposes behind much of this research are still unclear: whilst certain papers indicate the research may be to develop prophylactic measures, or other defensive techniques and strategies against "bio-threat" agents, other papers appear to indicate that at least certain activities may be intended for use in developing toxin weapons that will be used for "self-defence". Given such uncertainty, it is not possible to determine whether these research activities are consistent with the BTWC and CWC.

In 2016, researchers at the Molecular Biology and Genetic Engineering Laboratory, Defence Institute of Bio-Energy Research (DIBER) of

[33] Website of the Defence Research & Development Organisation, Ministry of Defence, Government of India, https://www.drdo.gov.in/about-drdo (accessed 5 January 2022).

[34] Sonkar, P. et al. (2020) Characterization of immune response induced against catalytic domain of botulinum neurotoxin type E. *Scientific Reports*, https://doi.org/10.1038/s41598-020-70929-8.

[35] Sehgal, P. et al. (2011) Differential toxicity profile of ricin isoforms correlates with their glycosylation levels. *Toxicology*, **282**(1–2), 56–67.

[36] Saxena, N. et al. (2018) Prophylactic efficacy of some chemoprotectants against abrin induced lethality. *Interdisciplinary Toxicology*, **11**(2), 169–177.

DRDO published a paper exploring the potential of selected "stinging plants and/or their biological toxins as novel bio-threat agents that maybe used for the development of bio-weapons for self-defence purpose".[37] The researchers stated that:

> Also, due to the Biological Weapons Convention (1972) international treaty that banned the use or stockpiling of most of the pathogenic bio-threat agents, which necessitate the search of some novel bio-threat agents like stinging plants that may be used as future biological weapon for self-defence. Therefore, in this effort, the Defence Institute of Bio-Energy Research (DIBER) is involved in the development of self-defence techniques/strategies against bio-threat agent outbreaks at our country border areas. DIBER is also actively engaged in the identification, characterization, detection and decontamination of several bio-threat agents. *Our efforts have led to the identification of several stinging plants that can be used for the formulation of the future novel bio-weapons for self-defence purposes* (Table 1)... (Emphasis added)[38]

The associated table listed a series of stinging plants of interest to the researchers, their mode of action, and component toxins, as well as prophylactic measures that can be employed against them. The paper concluded that:

> Therefore, they [stinging plants] may be used for the formulation of future novel bio-weapons. Future detailed work is required for identification and characterization of the precise stinging chemical components that will be used for the formulation of novel bio-weapons for self-defence purpose.[39]

A 2017 paper by researchers from Rajiv Gandhi University, the National Institute of Technology and DRDO, described their desk-based and field studies to collect and identify poisonous plant species in the Arunachal Pradesh State of northeast India.[40] The researchers noted that:

[37] Gupta, S. M. and Kumar, K. (2016) Stinging plants: as future bio-weapon, *Journal of Complementary and Integrative Medicine*, **13**(3), 217–219.

[38] Gupta, S. M. and Kumar, K. (2016) op. cit. p. 217.

[39] Gupta, S. M. and Kumar, K. (2016) op. cit. p. 219.

[40] Kalita, B. et al. (2017) Diversity and Traditional Uses of Some Poisonous Plants of Arunachal Pradesh. *International Journal of Advance Research and Innovative Ideas in Education*, **3**(1), 755–763.

> in the present state of global affairs where nuclear and chemical weapons are gaining popularity, *there is need to preserve … ancient knowledge on poisonous plants which was earlier used in traditional war tactics for self-defense, territorial and national security.* (Emphasis added)[41]

A literature review by the researchers of "ethnomedicinal plants … [showed] … that some plants are highly poisonous, however no specific research ha[d] been done on poisonous plants found in Arunachal Pradesh." The researchers' subsequent field investigations, which were conducted in 10 of the 18 districts of the State, identified 60 plants belonging to 37 families and 55 genera which were used for various poisoning purposes by the tribal people of Arunachal Pradesh. Herbarium specimens for all collected species were deposited in the Department of Botany, Rajiv Gandhi University for future reference. Although two of the four authors were from the Department of Botany, including the Head of Department, one of the other authors was described as "Scientist 'C' Defence Research Laboratory, DRDO, Ministry of Defence, Tezpur". The authors also thanked the Director of DRL Tezpur for facilities and partial funding of the work.

In 2018, a number of the same researchers published a paper describing their use of gas chromatography–mass spectroscopy (GC-MS) analysis of methanolic leaf extracts to investigate and identify bioactive phytochemicals of *Gynocardia odorata R.Br.*—a poisonous plant from the Arunachal Himalayan Region.[42] The researchers identified 50 compounds with a wide variety of psychopharmacological activities, some of which could contribute to the poisonous quality of the plant (which was commonly used as a fish poison by the local tribal communities). The researchers noted that "[T]oxicological study using acute and chronic models in animals is required to validate the toxicity effects of these phytocompounds on animal physiology."[43] This paper repeated the statement enunciated in the 2017 paper emphasising the need to preserve the ancient knowledge of poisonous plants "for self-defense, territorial and national security." Whilst the majority of the researchers were from Rajiv Gandhi University and the National Institute of Technology, the authors again included the

[41] Kalita, B. et al. (2017) op. cit. p. 755.

[42] Kalita, B. et al. (2018) GC-MS analysis of phytocomponents in the methanolic extract of *Gynocardia odorata* R.Br.—A poisonous plant from Arunachal Himalayan Region. *Journal of Pharmacognosy and Phytochemistry*, 7(1), 2458–2463.

[43] Kalita, B. et al. (2018) op. cit. p. 2460.

"Scientist 'C' from the Defence Research Laboratory, Tezpur. In addition, the authors again thanked the Director of DRL Tezpur, Assam for facilities and encouragement and for partial funding support during field work.

A subsequent 2019 field study by researchers from Rajiv Gandhi University was conducted into the use by Arunachal Pradesh tribal communities of additional plant species. This study did not include researchers from DRDO and appeared to be predominately exploring medicinal value of these plants; however, it did identify further plants harmful to humans causing "allergy, nausea, itching, fever, and death, in severe cases".[44]

In 2018 researchers from DIBER/DRDO published a paper in the *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, describing their "phytochemical analysis of stinging plants and/or their biological toxins as novel future bio-threat agents that may be used for self-defence purpose".[45] They argued that:

> The stinging plant based products are used as novel biothreat agent that can also be used intentionally against humans, plants or animals to cause disease, fear, death, societal disruption and economic detriment of the nation for self defence. It has several advantages over other bio-threat agents (nuclear and chemical warfare agents and pathogens).[46]

Furthermore, the authors continued by arguing that because the BTWC "banned the use or stockpiling of most of the pathogenic bio-threat agents" this will "necessitate to search some novel natural bio-threat agents from stinging plants that may be used as future bio-weapon for self-defence purposes".[47] The researchers also stated that "[T]he objective of the present study is to identify, characterize and screen the potential of Indian stinging plants on the basis of their secondary metabolite contents that may be used for the formulation of novel future bio-threat agents for self-defence."[48] The researchers detailed how their research examining "stinging plants as

[44] Wangpan, T. et al. (2019) Traditional use of plants as medicine and poison by Tagin and Galo Tribe of Arunachal Pradesh. *Journal of Applied Pharmaceutical Science*, **9**(9), 98–104. p. 98.

[45] Gupta, S. M. et al. (2018a) Phytochemical Analysis of Indian Stinging Plants: An Initiative Towards Development of Future Novel Biothreat Agents for Self-defence. *Proceedings of the National Academy of Sciences, India Section B: Biological Sciences*, 88(2), 819–825.

[46] Gupta, S. M. et al. (2018a) op. cit. p. 820.

[47] Gupta, S. M. et al. (2018a) op. cit. p. 820.

[48] Gupta, S. M. et al. (2018a) op. cit. p. 820.

potential source for isolation of toxic compounds towards development of future novel bio-threat agents for self-defence … led to the identification of several stinging plants from different regions of India".[49] These plants were then "further screened on the basis of their secondary metabolite contents that mainly include phenolics (total phenol, flavonoids, tannins), terpene (terpenoids and essential oils) and nitrogen containing compounds (alkaloids) for selecting candidate plant for the development of future novel bio-threat agents for self-defence."[50] The researchers identified *M. pruriens* as having the "best potential for harvesting of toxic secondary metabolite compounds for the formulation of future novel bio-threat agents for self-defence purpose".[51] *Mucuna pruriens* is described by the common name Velvet bean or Cowitch. The authors indicated that "future detailed work is required for identification and characterization of the precise toxic stinging compounds from potential stinging plant by using advanced gas chromatography–mass spectrometry (GC–MS) methods."[52] The authors were identified as being from DIBER with two acknowledging support from DRDO for the study. Concerns regarding this research are deepened by the authors' apparent reading of the BTWC presumably to the effect that weaponisation of such toxins for self-defence is allowable as a peaceful purpose and therefore that such activities are permitted under the Convention. This is a reading of Article 1 of the Convention that would surely open the door to the eventual erosion of the prohibition. This situation is further exacerbated as the research was funded and carried out by DIBER/ DRDO and the paper published under the auspices of the Indian National Academy of Science. This raises troubling questions regarding the effectiveness of ethical review processes in place in these organisations.

In 2018 DRDO researchers published a paper[53] describing their continuing investigations into Himalayan region plants that produce "toxins that have the ability to adversely affect human health in a variety of ways, ranging from relatively mild allergic reactions to serious medical complications, including death". They stated that[54]:

[49] Gupta, S. M. et al. (2018a) op. cit. p. 822.
[50] Gupta, S. M. et al. (2018a) op. cit. p. 822.
[51] Gupta, S.M. et al. (2018a) op. cit. p. 824.
[52] Gupta, S. M. et al. (2018a) op. cit. p. 824.
[53] Gupta, S. M. et al. (2018b) Himalayan Toxic Plants of Defense Importance. *ACTA Scientific Medical Sciences*, **2**(3), 44–48.
[54] Gupta, S. M. et al. (2018b) op. cit. p. 44.

> This concept paper proposes the use of many toxic plant resources of the Himalayan region that may be exploited for the development of novel multi-system targeted agents for self-defence by using various biotechnological tools.

They then illustrate their concept in a diagram as shown here in Fig. 4.1.

The researchers stated that "[O]ur efforts have led to the identification of several poisonous plants that can be used for *the development of novel*

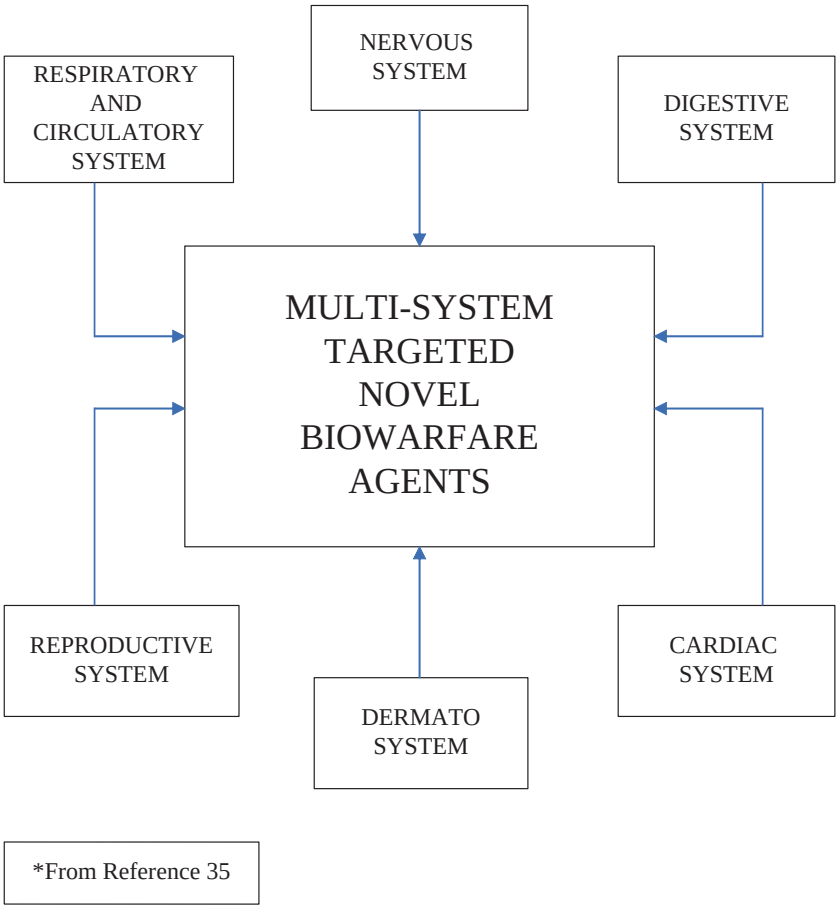

Fig. 4.1 Concept for development of multi-system targeted agents for defensive applications

multi-system targeted warfare agents for defensive applications" (emphasis added). The paper examined ten candidate plants: *Heracleum canescens*, *Delphinium brunonianum*, *Silybum marianum*, *Aconitum chasmanthum*, *Melia azedarach*, *Convallaria majalis*, *Solanum xanthocarpum*, *Hyoscyamus niger*, *Arisaema triphyllum*, and *Cannabis sativa*.[55] The researchers noted that such plants "have harmful effect on various biological systems like nervous, cardiac, digestive, respiratory, dermal, etc simultaneously".[56] Some of these plants contain compounds that would be likely to cause serious health effects if used against people. For example, the researchers list *Aconitum chasmanthum* as containing aconitines that would have neurotoxic and gastrointestinal effects. Aconitine would certainly cause such effects.[57] The researchers recognised that "future detailed work is required for identification and characterization of the precise toxic chemical components" that "*may be used for the formulation of future novel multi-system targeted defensive warfare agents*" (emphasis added).[58] The researchers argued that the use of various poisonous plants for the "development of multi-system targeted novel warfare defensive agents" had several advantages over "other warfare agents like… microbial and chemical warfare agents". They argued that "[L]ocally grown poisonous plants are easier and cheaper to multiply and sustain in the natural environment. They are … lethal to animals … livestock … humans and prove to be effective agents for self-defense."[59] Once again this was a multi-institute research project, with three of the authors coming from DIBER/DRDO and one from DRL Tezpur; and with the paper thanking DRDO HQ, New Delhi, for providing financial support for one of the authors.

4.6 CWC Article X Declarations and the BTWC Confidence-Building Measures

Under both the BTWC and the CWC, States Parties are permitted to conduct research and associated activities including the production of appropriate quantities of potential weapons agents for "prophylactic,

[55] Gupta, S. M. et al. (2018b) op. cit. pp. 45–46.

[56] Gupta, S. M. et al. (2018b) op. cit. p. 44.

[57] Gao, X. et al. (2020) Research progress of aconitine toxicity and forensic analysis of aconitine poisoning. *Forensic Science Research*, **5**(1), 25–31.

[58] Gupta, S. M. et al. (2018b) op. cit. p. 47.

[59] Gupta, S. M. et al. (2018b) op. cit. pp. 44.

protection and other purposes" under the BTWC, and for "protective purposes" under the CWC. Recognising the danger that such activities could mask weapons programmes, both the OPCW and the BTWC States Parties have introduced relevant reporting and transparency mechanisms. Consequently, CWC States Parties are required under Article X of the Convention to provide annual declarations to the OPCW Technical Secretariat on "national programmes related to protective purposes". There is currently no requirement to make Article X declarations public, and India has not done so.[60]

Similarly, to enhance transparency, BTWC States Parties agreed to submit annual confidence-building measure (CBM) reports from 1987 to the States Parties/ISU on relevant national activities. According to the UNOG/ISU database, prior to 2009, Indian submitted its CBM reports in 1997 and 2007. Since 2009, India has submitted CBMs to the BTWC States Parties/ISU on an annual basis, with the latest CBM submitted in 2022. However, none of these CBMs are publicly available.[61]

Consequently, it is not possible for civil society to directly establish whether India has reported to either the OPCW or BTWC States Parties/ISU on toxin and bioregulator research and other related activities undertaken by DRDO and related institutions, and if so, whether it has identified them as being for protective or other permitted purposes.

Despite requests from the authors to the relevant Indian government representatives for information on the research highlighted in this case study, no response was forthcoming.

4.7 Concluding Remarks

There is no evidence that India has developed, acquired, stockpiled, or employed toxin or bioregulator-based weapons specifically intended for armed conflict. Indian law enforcement bodies have developed or acquired 'wide area' RCA means of delivery, a number of which are potentially capable of disseminating OC (a sensory irritant of biological origin) and PAVA (a synthetic capsaicinoid), over large areas or extended distances. India should provide details of which, if any, Indian military, security, or

[60] OPCW, *CWC* (1993) op. cit. Article X, paragraph 4.

[61] United Nations, *Confidence Building Measures, India*. https://bwc-ecbm.unog.ch/state/india. Accessed 23 April 2022.

police forces possess stocks of these means of delivery, the nature of such stockpiles; and the circumstances under which such means of delivery would be employed. Indian scientists, including those associated with the DRDO, have undertaken research into a range of malodorants apparently with the intention of developing them for use in law enforcement crowd dispersal operations. DRDO scientists have also undertaken research into pharmaceutical chemicals that could have dual-use application in relation to ICA/CNS-acting agents.

In addition, military and military-related and funded institutions and scientists have recently searched for, identified, and characterised toxins and other substances from a broad range of indigenous Indian stinging and other poisonous plants. Contemporary scientific papers published by these researchers describe their work as being associated with the potential "formulation of novel future bio-threat agents for self-defence" or alternatively of being "exploited for the development of novel multisystem targeted agents for self-defence". Some of the toxins investigated as potential 'agents' are highly toxic and could be lethal; others though not as toxic could still potentially be employed as "less lethal" toxin weapons. It is not possible from the available open-source information to assess whether these activities are consistent with India's obligations under the BTWC and CWC, though the information currently available raises concerns that this may not be the case.

It would be beneficial if India made public full information about the contemporary dual-use research activities identified in this case study, including details of all potential agents identified, whether stocks of such agents are held, and if so in what form and for what purposes. Furthermore, India should explain how such activities are consistent with its obligations under the BTWC and CWC. India should also clarify whether such activities have been fully detailed in its annual CBM reports to the ISU/BTWC States Parties and whether India has reported such activities to the OPCW in any Article X reports it has submitted. To promote transparency and public confidence in this area India should publicly release the details of relevant BTWC CBM and CWC Article X reports detailing such activities.

CHAPTER 5

The Iran Case Study

5.1 Changing Perceptions of Alleged Iranian Biological and Toxin Weapon Programmes

Iran acceded to the Geneva Protocol in 1952 and ratified the Biological and Toxin Weapons Convention (BTWC) in 1973. It subsequently ratified the Chemical Weapons Convention (CWC) in 1997. Iran has repeatedly affirmed its rejection of all weapons of mass destruction (WMD). For example, in 2005, in its formal response to the UN Committee assessing implementation of UN Security Council Resolution 1540, Iran declared that "[T]he Islamic Republic of Iran considers acquiring, developing, and using WMD as inhumane, immoral, illegal, and against its very basic principles."[1] However, despite such avowals, conflicting high-level Iranian statements concerning chemical and biological weapons (CBW), and reported dual-use research activities undertaken by Iranian chemical and life scientists, have given rise to long-standing concerns that Iran had initiated a biological and toxin weapons programme.

During the 1980s there were reported statements by leading Iranian government figures indicating Iran's intentions to develop chemical and

[1] United Nations Security Council, Security Council, Committee established pursuant to resolution 1540 (2004), *Note verbale dated 28 February 2005 from the Permanent Mission of the Islamic Republic of Iran to the United Nations addressed to the Chairman of the Committee*. S/AC.44/2004/(02)/105, 1 March 2005.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_5

biological weapons. In April 1986 Moshan Rafiqdust, the Minister of the Iranian Republican Guard Corp (IRGC) reportedly stated that:

> The *armament industries of the Corps have made notable progress in* the missile, aircraft, *biological, chemical*, and nuclear *fields* as well as in construction of engineering equipment such as a variety of bridges, mortar-launchers, and rocket-propelled grenades. (Emphasis added)[2]

In 1988, Hashemi-Rafsanjani, then Acting Commander in Chief of the Armed Forces as well as Speaker of the Islamic Consultative Assembly (or Majlis), was reported to have announced during an October 1988 speech:

> *We should fully equip ourselves both in the offensive and defensive use of chemical, bacteriological*, and radiological *weapons*. From now on, you should make use of the opportunity and perform this task. (Emphasis added)[3]

During the 1990s and early 2000s, certain States, notably the US, repeatedly alleged that Iran had breached its commitments under the Biological and Toxin Weapons Convention (BTWC). According to a report by the US Central Intelligence Agency (CIA) to the US Senate in 1996, "[I]ran has had a biological warfare program since the early 1980s. Currently the program is in its research and development stages, but we believe Iran holds some stocks of BW agents and weapons."[4] In its 2003 *Arms Control Compliance Report*, the US stated that: "[I]ran has an offensive biological weapons program in violation of the BWC. Iran is technically capable of producing at least rudimentary biological warheads for a variety of delivery systems, including missiles." Similar assertions were made by the US

[2] FBIS, Tehran Domestic Service, "Domestically Produced Mortar Shells Sent to Fronts," interview with Moshan Rafiqdust, Minister of the IRGC, as cited in, Desutter, P. (1995) *Denial and jeopardy: deterring Iranian use of NBC weapons*, NDU. Available from the US Centre for Homeland Defense website at https://www.hsdl.org/?abstract&did=3599 and also from the Federation of American Scientists website, at https://nuke.fas.org/guide/iran/doctrine/dajd/ch3.html.

[3] As quoted in United States (2005) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. State Department, August. p. 20.

[4] United States, Central Intelligence Agency (1996) *Current and Projected National Security Threats to the United States and its Interests Abroad: Written responses to questions before the Select Committee on Intelligence of the United States Senate*. Hearing 104–510, 22 February. Available at https://fas.org/irp/congress/1996_hr/s960222n.htm. p. 82.

in its 2005 *Arms Control Compliance Report*.[5] Contemporaneous analysis by certain civil society arms control organisations and researchers generally aligned with these US threat perceptions.[6]

Whilst the US has been the most consistent and explicit in its accusations of Iranian biological weapons development, certain other States have raised similar concerns. In February 2005, the German Customs Office of Criminal Investigations (ZKA) reported that Iran was engaged in "biological weapons programs" being conducted "in small laboratories of universities, strictly guarded from the outside world." The ZKA also stated that "[I]ran has long-standing experience in the field of bio-technology so that is has the necessary know-how for operating biological combat agent programs."[7]

Subsequent reports from US intelligence agencies and from the US government were more cautious in their appraisal of later Iranian activities and intentions. In its 2010 *Arms Control Compliance Report*, the US stated that:

> Iran *may not* have ended activities prohibited by the BWC, although available information does not *conclusively* indicate that Iran is currently conducting activities prohibited by the Convention. (Emphasis added)[8]

A 2011 report from the US Director of National Intelligence (DNI) stated that:

[5] United States (2003) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*, State Department, p. 10; United States (2005) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. State Department, August, p. 21.

[6] See for example Leitenberg, M. (2005) *Assessing the Biological Weapons and Bioterrorism Threat*, Strategic Studies Institute, December; Cordesman, A. and Seitz, A. (2008) *Iranian weapons of mass destruction: biological weapons programs, Working Draft for Review and Comments*, 28 October; NTI (2020) *Iran, Biological*. Last updated January 2020, https://www.nti.org/learn/countries/iran/biological/.

[7] *German intelligence services see Iran possessing biological, chemical weapons*, 20 February 2005. FBIS document EUP2005022000035, www.opensource.gov, as cited in Cordesman, A. and Seitz, A. (2008) op. cit.p. 8.

[8] United States (2010) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments (Arms Control Compliance Report, ACCR)*. State Department, July.

> Iran *probably* has the capability to produce some biological warfare (BW) agents for offensive purposes, if it made the decision to do so. We assess that Iran has previously conducted offensive BW agent research and development. Iran continues to expand its biotechnology infrastructure and seek dual-use technologies that *could* be used for BW. (Emphasis added)[9]

In its 2015 *Arms Control Compliance Report*, the US concluded that "available information indicated that Iran continues to engage in dual-use activities with BW applications, but *it is unclear* if these activities were conducted for purposes inconsistent with the BWC" (emphasis added).[10]

After a four-year hiatus when no US *Arms Control Compliance Reports* were forthcoming, more recent US threat perceptions of Iranian intentions seemed to have once again hardened. In its *Arms Control Compliance Reports* from 2019 till 2022, the US contended that:

> *Iran has not abandoned its intention to conduct research and development of biological agents and toxins for offensive purposes.* This is based on a cumulative assessment of current and past Iranian activity and its continued lack of transparency. (Emphasis added)[11]

The US further contended that:

> Iran maintains flexibility to use, upon leadership demand, legitimate research underway for biodefense and public health purposes for a capability to produce lethal BW agents; whether maintaining this flexibility is pursuant to decisions by leadership is unknown. The United States remains unable to

[9] United States (2011) *Unclassified Report to Congress on the Acquisition of Technology Relating to Weapons of Mass Destruction and Advanced Conventional Munitions, Covering 1 January 1 to 31 December 2011.* US Director of National Intelligence, p. 4. Available at http://fas.org.

[10] United States (2015) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, 5 June.

[11] United States (2022) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, April, p. 36; United States (2021) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, April, p. 47; essentially identical assessments were detailed in United States (2020) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, June, pp. 57–58; and United States (2019) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, August, pp. 46–47.

> differentiate some of Iran's public health research and biodefense activities from those that are prohibited under the BWC, complicating assessments of Iranian compliance.[12]

It should be noted that the US publicly provided limited evidence to support the allegations it made concerning perceived Iranian biological and toxin weapons-related activities, including in the unclassified versions of its *Arms Control Compliance Reports*. It is not known whether further information is provided in the classified versions of such reports.

5.2 Alleged Toxin Weapon Development

Publicly available information providing specific details concerning Iran's previous alleged biological and toxin weapons-related activities and possible biological and toxin agents developed have been sparse and unsubstantiated, coming primarily from media and civil society researchers. In April 1989, the *New York Times* journalists Gordon and Engelberg reported unsuccessful separate attempts by Iranian scientists apparently from the Imam Reza Medical Center and the Iranian Research Organization for Science and Technology to acquire fungal strains including *Fusarium* (a fungus that produces T-2 mycotoxins) from Canada and the Netherlands, respectively.[13] Given the potential utility of T-2 mycotoxins as toxin weapons, such attempted procurement raised concerns among both State and civil society non-proliferation communities; however, the intention behind such activities was never established.[14]

According to the Nuclear Threat Initiative (NTI) "[R]eports in the early 1990s claimed, without citing specific sources, that Iran at one time pursued the acquisition of castor beans (known to be used for producing the deadly toxin ricin[15]), and that it additionally worked to develop

[12] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) op. cit. p. 47; United States Arms Control Compliance Report (2022) op. cit. p. 36.

[13] Gordon, M. and Engelberg, S. (1989) Iran Is Said to Try to Obtain Toxins. *The New York Times*, 13 August 1989. Available at https://www.nytimes.com/1989/08/13/world/iran-is-said-to-try-to-obtain-toxins.html.

[14] NTI, *Iran, Biological*, last updated January 2020. Available at https://www.nti.org/learn/countries/iran/biological/.

[15] Whilst the outer casing of Castor beans contains the toxin, ricin, the beans themselves have certain medicinal applications and Castor oil can be employed for other peaceful purposes such as engine lubrication.

botulinum toxin and anthrax…. These claims, however, remain unsubstantiated."[16] In their 2008 report, Cordesman and Seitz stated that "U.S. experts indicate that Iran might have begun to stockpile anthrax and botulinum in a facility near Tabriz, can now mass manufacture such agents, and has them in an aerosol form. None of these reports, however, can be verified."[17]

More detailed allegations concerning Iranian biological and toxin weapons programmes have also been published by Iranian opposition organisations though their veracity has been repeatedly questioned and cannot be substantiated.[18]

5.3 Contemporary Dual-Use Toxin Research, Development, and Production

Iran has an established and growing biotechnology research, development, and production sector that is one of the most advanced in the developing world. Iran has long been recognised as a regional leader in agricultural biotechnology, pharmaceutical chemical manufacture, and vaccine research and development. According to NTI, it runs three internationally renowned health research facilities, the Pasteur Institute of Iran, and the National Research Center of Genetic Engineering and Biotechnology (NRCGEB), which focus on human health; and the Razi Institute for Serum and Vaccines, which studies both human disease and zoonoses. All three facilities host advanced microbiology and genetic engineering equipment and expertise.[19] The scale of Iranian commercial production in this area is significant, with, for example, the Razi Institute in

[16] NTI, *Iran, Biological*, last updated January 2020. Available at https://www.nti.org/learn/countries/iran/biological/.

[17] Cordesman, A with Seitz, A. (2008) op. cit. p. 4.

[18] See for example: *Iranian Regime's Programs for Biological and Microbial Weapons*, Press Briefing by Soona Samsami and Alireza Jafarzadeh, 15 May 2003. Available from https://www.iranwatch.org/library/ncri-iranian-regimes-programs-biological-weapons-5-15-03; for further discussion see Cordsman, A. with Seitz, A. (2008) op. cit. pp. 8–11.

[19] NTI (2020) *Iran, Biological.* Last updated January 2020 Available at https://www.nti.org/learn/countries/iran/biological/.

2008 reported to have been manufacturing 1.7 billion doses of 57 types of vaccines, serums, and antigens on an annual basis.[20]

In addition to the commercial sector, Iran has an extensive network of respected medical, life science, and chemical research laboratories based in its universities. This includes a number of universities controlled by the Iranian Revolutionary Guard Corps (IRGC) which are run along military lines. Researchers and departments in certain IRGC Universities have been accused of having undertaken clandestine nuclear weapons research and been placed on UN and national sanctions lists.

There have been long-running concerns voiced by the US and certain civil society observers with regard to the potential for the misuse of Iran's life science infrastructure in research, development, and production of biological and toxin weapons. In its 2005 *Arms Control Compliance Report*, the US essentially repeated the claim it previously made in its 2003 report, stating that:

> The Iranian BW program has been embedded within Iran's extensive biotechnology and pharmaceutical industries so as to obscure its activities. The Iranian military has used medical, education, and scientific research organizations for many aspects of BW-related agent procurement, research, and development.[21]

In its 2010 *Arms Control Compliance Report*, the US claimed that: "[A]vailable information…indicates Iran has remained engaged in dual-use activities that include procuring dual-use biological equipment and materials, conducting research involving BW-related pathogens and genetic engineering, and developing mechanisms that could be used to deliver biological agents."[22]

In 2010, the Federation of American Scientists (FAS) published a survey of dual-use research conducted by life and chemical scientists from

[20] According to NTI, "[T]he institute is considered Iran's leading center for biological research and production. It manufactures 21 human and veterinary vaccines in commercial quantities and several other biological substances. The institute exports human and animal vaccines to more than 16 countries (mostly Moslem countries) as part of Iran's humanitarian aid program." NTI (2008) Razi Institute for Serums and Vaccines. Last updated 1 August 2008. Available at https://web.archive.org/web/20200413231148/https://www.nti.org/learn/facilities/314/.

[21] Unite States Arms Control Compliance Report (2003) op. cit.; United States Arms Control Compliance Report (2005) op. cit.

[22] United States Arms Control Compliance Report (2010) op. cit.

three "IRGC Universities"—Baqiyatallah University of Medical Sciences (BMSU), Imam Hossein University (IHU), and Malek Ashtar University of Technology.[23] Among the toxin-related papers that FAS identified were descriptions of cloning and expression of DNA fragments encoding parts of botulinum neurotoxins A and E,[24] and *Pseudomonas aeruginosa* exotoxin;[25] examination of the mechanism of T-2 toxin activity;[26] factors effecting *Clostridium botulinum* Type A production and activity;[27] and analysis of the biological effects of Type B staphylococcus enterotoxin.[28] A second 2010 FAS survey of "Iranian Dual-Use CBW [chemical and biological weapons] Related Technology" highlighted papers from a broader range of research establishments[29] including further investigation of botulinum neurotoxins A and E, and gene coding and cloning of specific domains;[30] investigation of T-2 toxin toxicity;[31] cloning and expression of cholera toxin B subunits;[32] and purification of diphtheria toxin.[33]

The current authors have identified further research by scientists from certain IRGC Universities into 'classic' toxins. A 2011 paper by IHU scientists described extraction of ricin, subsequent cloning and expression of

[23] Gorwitz, M (2010) *Iranian Dual-Use Science and Technology Bibliography, Volume II: IRGC Universities*. Federation of American Scientists, December.

[24] Mousavi, M. et al. (2004) Cloning, Expression and Purification of *Clostridium botulinum* Neurotoxin Type E Binding Domain. *Iranian Journal of Biotechnology*, **2**, 183–188.

[25] Bayat, K. et al. (2010) Isolation, Determination and Cloning of Translocation Domain of Exotoxin from *Pseudomonas Aeruginosa*. *Kowsar Medical Journal*, **15**, 149–154.

[26] Ahmadi, K. and Riazipour, M. (2007) Effect of T-2 Toxin on Cell Death and Nitric Oxide Release by Mice Peritoneal Macrophages. *Journal of Military Medicine*, **9**, pp. 1–6.

[27] Behzadian, N.et al. (2000–2001) The Effect of Zinc's Chelator on *Clostridium botulinum* Type A Toxin Activity. *Daneshvar Medicine*, **8**, 45–52.

[28] Fouladi, A. et al. (2004) Biological Effects of Type B Staphylococcus Enterotoxin. *Kowsar Medical Journal*, 2004.

[29] Gorwitz, M. (2010) *Iranian Dual-Use CBW Related Technology, Iranian Dual-Use Science and Technology Bibliography, Volume III: CBW Related Research*. Federation of American Scientists, December.

[30] Tavallaie, M. et al. (2000) Cloning of Binding Domain of *Clostridium Botulinum* Type A in *Escherichia coli*. *Archives of the Razi Institute*, **51**, 13–21.

[31] Daraei, B. et al. (2004) H. T-2 Toxin Hepatotoxicity in the In Situ Rat Liver Model. *Iranian Journal of Pharmaceutical Research*, **3**, 225–230.

[32] Arzanlou, M. et al. (2005) Expression of Cholera Toxin B Subunit in *Saccharomyces cerevisiae*. *Annals of Microbiology*, 55, 145–150.

[33] Zolfagharian, H. and Mohammadpour, N. (2004) Study on Diphtheria Toxin Purification: A New Approach to Prepare Toxoid. *Archives of the Razi Institute*, **57**, 65–74.

the toxin's B chain, and exploration of its antigenicity in mice,[34] whilst a 2017 paper co-authored by an IHU researcher explored the mechanism of ricin toxicity, methods of diagnosis, treatment, and potential new vaccine candidates.[35] A 2018 paper by IHU researchers described their cloning and recombinant expression of *Staphylococcus aureus* enterotoxin B (SEB) with the purpose of exploring it as a vaccine candidate,[36] whilst a 2020 paper by IHU researchers described nasal administration to mice of recombinant SEB protein nanoparticles to explore their immunogenicity.[37]

A particular focus of scientists from certain IRGC universities has been botulinum toxin. Papers published in 2004,[38] 2005,[39] 2009,[40] 2014,[41] 2016,[42] and 2018[43] by teams that included BMSU and IHU researchers described the cloning and expression of botulinum neurotoxin A, B, or E fragments, including their binding and catalytic domains. Related research at other Iranian universities has included production and characterisation

[34] Sadraeian, M. et al. (2011) Extraction, Cloning and Expression of RTB, as a Vaccine Adjuvant/Carrier, in *E. coli* and Production of Mouse Polyclonal Antibody (Anti-B chain Abs), *Iranian Journal of Pharmaceutical Sciences*, **7**(4), 247–254.

[35] Sadeghi, D. et al. (2017) Ricin toxin: mechanisms of toxicity, diagnosis methods, treatment and immunization against it. *Jundishapur Scientific Medical Journal*, **16**(1), 103–124.

[36] Hosseini, S. et al. (2018) Recombinant Expression of Staphylococcus aureus Enterotoxin Type B as a Vaccine Candidate. *Jundishapur Scientific Medical Journal*, **16**(6), 653–664.

[37] Hosseini, S. et al. (2020) Immunogenicity Evaluation of Recombinant *Staphylococcus aureus* Enterotoxin B (rSEB) and rSEB-loaded Chitosan Nanoparticles Following Nasal Administration. *Iranian Journal of Allergy, Asthma, and Immunology*, **19**(2), 159–171.

[38] Mousavi, M. et al. (2004) Cloning, expression and purification of *Clostridium botulinum* neurotoxin type E binding domain. *Iranian Journal of Biotechnology*, 2(3), July 2004, 183–188.

[39] Mossavi, M. et al. (2005) Cloning, expression and purification of the gene coding translocating domain of Botulinum Neurotoxin type A. *Modares Journal of Medical Sciences*, **7**(2), 81–92.

[40] Mansour A. A. et al. (2010) Cloning, high level expression and immunogenicity of 1163–1256 residues of C-terminal heavy chain of *C. botulinum* neurotoxin type E. *Biologicals*, **38**(2), 260–264.

[41] Rezaeiani S. et al. (2014) Cloning and expression of *Clostridium Botulinum* Type B binding domain *E.Coli*. *Studies in Medical Sciences*, **25**(6), 502–510.

[42] Saffarian, P. et al. (2016) Evaluation of the expression of recombinant type A Botulinum neurotoxin light chain loaded onto a cell-penetrating peptide. *Journal of Babol University of Medical Sciences (JBUMS)*, **18**(1), 25–30.

[43] Aghaie, S. et al. (2018) Expression and Purification of Recombinant Catalytic Domain of Botulinum Neurotoxin Type E from a Synthetic Gene. Pathobiology Research, **21**(2), 79–84.

of a recombinant chimeric antigen consisting of botulinum neurotoxin serotypes A, B, and E binding subdomains.[44]

In addition to university-based research, there are indications of production of botulinum toxin. Although it does not identify the facility concerned, the US in its 2019–2022 *Arms Control Compliance Reports* stated that "Iran has engaged in dual-use activities with potential for BW applications such as building a plant for pharmaceutical botulinum toxin production", which the US reports clarified was for "commercial production".[45]

Iran clearly has a variety of endemic venomous species and good reason to investigate them and the venoms they produce for medicinal and other legitimate purposes. Certain aspects of such research may potentially have malign applicability, and the current authors have identified Iranian dual-use research into such novel toxins. For example, 2007 and 2008 papers from teams that both included scientists from the Pasteur Institute of Iran and Razi Vaccine and Serum Research Institute, described discovery, sequencing, and characterisation of action of two new toxins, hemicalcin and hemitoxin, both obtained from the Iranian scorpion *Hemiscorpius lepturus*.[46] A 2017 paper by a team including Pasteur Institute of Iran researchers identified a potentially lethal phospholipase D toxin from the venom of *Hemiscorpius lepturus*. A recombinant isoform of this toxin (Hl-RecPLD1) was cloned, expressed, and purified.[47] A 2020 paper by a similar team examined the protection against this toxin afforded by anti-Hl-RecPLD1 Immunoglobulin G.[48] Papers published in 2019 and 2021 described the subcloning and expression of antigens derived from the

[44] Ebrahimi, F. et al. (2010) Production and characterization of a recombinant chimeric antigen consisting of botulinum neurotoxin serotypes A, B and E binding subdomains. *Journal of Toxicological Sciences*, **35**(1), pp. 9–19.

[45] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) p. 48; United States Arms Control Compliance Report (2022) op. cit. p. 36.

[46] Shahbazzadeh, D. et al. (2007) A new toxin from the Iranian scorpion *Hemiscorpius lepturus* which is active on ryanodine-sensitive Ca2+ channels. *Biochemical Journal*, **404**(1), 89–96.; Srairi-Abid, N. et al. (2008) Hemitoxin, the first potassium channel toxin from the venom of the Iranian scorpion *Hemiscorpius lepturus. FEBS*, **275**(18), 4641–4650.

[47] Torabi, E. et al. (2017) Characteristics and Lethality of a Novel Recombinant Dermonecrotic Venom Phospholipase D from *Hemiscorpius lepturus. Toxins*, **9**(3), p. 102.

[48] Torabi, E. et al. (2020) Complete neutralization of the lethality of *Hemiscorpius lepturus* crude venom by a novel anti-recombinant phospholipase D1 IgGs. *Toxicon*, **183**, 36–43.

venom of the box jellyfish *Chironex fleckeri* and assessment of their antigenicity in mice.[49]

In its 2019–2022 *Arms Control Compliance Reports*, the US stated that "Iranian biotechnology entities, particularly military-affiliated institutions, continued to pursue dual-use technologies" and specifically that "[O]pen source reports note Iranian military-associated universities and affiliated research centers have conducted BW relevant projects on bioregulators."[50] Although the 2019–2022 US *Arms Control Compliance Reports* provided no further information, an open-source review by the current authors identified contemporary research by IRGC University researchers into bioregulators and other biologically active peptides. Two 2016 papers by BMSU researchers described isolation of high affinity ssDNA aptamers binding and inhibiting the bioregulator peptide angiotensin II (Ang II) and further described investigation of aptamer bioactivity in cellular and animal models;[51] a 2016 paper by a team including IHU researchers described the modulation of the GABAergic system by natural terpenoids and the potential for treating neurological diseases;[52] whilst a second 2016 paper by a team including IHU and BMSU researchers synthesised and studied selective GABA(A) agonists.[53]

In addition to investigating specific bioregulators and bio-regulatory processes, a 2019 paper from an Iranian research team including BMSU scientists provided an overarching review of the properties and potential applications of bioregulators including as bioweapons, and the consequent implications for Iranian biodefence. Although the full paper is only available in Farsi, the English abstract stated:

[49] Jafari, H. et al. (2021) Cloning and Expression of N-CFTX-1 Antigen from *Chironex fleckeri* in *Escherichia coli* and Determination of Immunogenicity in Mice. *Iranian Journal of Public Health*, **50**(2), 376–383.

[50] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) op. cit. p. 48; United States Arms Control Compliance Report (April 2022) op. cit. p. 36.

[51] Heiat, M. et al. (2016) Computational approach to analyze isolated ssDNA aptamers against angiotensin II. *Journal of Biotechnology*, **230**, 34–39; Heiat, M. et al. (2016) Selection of a high-affinity and in vivo bioactive ssDNA aptamer against angiotensin II peptide. *Peptides*, **82**, 101–108.

[52] Manayi, A. et al. (2016) Natural terpenoids as a promising source for modulation of GABAergic system and treatment of neurological diseases. *Pharmacological Reports*, **68**, 671–679.

[53] Taghizadeh, M. J. et al. (2017) Synthesis and docking study on thiadiazolo[3,2-a][1,3]diazepin-8(5H)-one derivatives as selective GABA(A) agonists. *Journal of Sciences*, **4**(2), 101–108.

> The military applications of these agents [bioregulators] in the production of a new generation of biological weapons with the aim of temporarily disabling the enemy are of great interest…. It is suggested that bioregulators as important agents in hostage-release processes or factors that advance military objectives, both during military operations and in support of those involved in the battlefield have been mass-produced and placed at the disposal of certain forces…. Until now several bioregulators as potential factors in the production of biological weapons-debilitating have been introduced. *Therefore, our Armed Forces need to become familiar with the application of these factors to maintain and enhance the preparedness and provide the necessary strategies for identifying, neutralizing, and treating those involved with these factors.* (Emphasis added)[54]

The 2019–2022 US *Arms Control Compliance Reports* have underlined the difficulties for compliance assessment due to the dual-use nature of the technologies being studied: "[T]he [US] remains unable to differentiate some of Iran's public health research and biodefense activities from those that are prohibited under the BWC, complicating assessments of Iranian compliance."[55] However despite these caveats, the US contended that "the nature of Iran's sophisticated toxin research and production and its capability to produce lethal agents on demand raise concerns regarding Iran's compliance with its obligations under Article I of the BWC."[56]

5.4 Riot Control Agents and Incapacitating Chemical Agents/CNS-Acting Agents

Iranian law enforcement officials possess and employ hand-held sprayers which disseminate an unidentified "pepper spray" in limited quantities and over relatively small areas. If employed in appropriate amounts and circumstances, they would appear to be consistent with the BTWC and CWC. However, there have been reports of excessive or inappropriate use of such 'limited area' pepper spray means of delivery by Iranian law

[54] Latifi, A. et al. (2019) Bioregulators, Properties and Their Applications. *Paramedical Sciences and Military Health*, **14**(1), 56–68.

[55] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) op. cit. p. 47; United States Arms Control Compliance Report (2022) op. cit. p. 36.

[56] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) op. cit. p. 48; United States Arms Control Compliance Report (2022) op. cit. p. 36.

enforcement officials. Such practice would appear to contravene relevant human rights law and standards.[57] In addition, at least one Iranian company, Shahid Meisami Group, (SMG) that markets riot control agents, has been reported to have promoted a means of delivery of potential concern. In its *2020–2022 CWC Compliance Reports*, the US asserted that SMG had "provided fact sheets to interested users on a "Fog Maker System" that can be used to make smoke and fog at high volume in a short time".[58] The *Compliance Reports* include images from an undated "Iranian advertisement" for a "Fog Maker" mounted on a speed boat and a truck. According to the US, "this is noteworthy because it can disseminate debilitating chemicals, like [the RCA] CR, over a large area quickly."[59] Although no further details are publicly available, the SMG system appears potentially capable of dispersing a range of RCAs, including OC and its synthetic analogues, over wide areas.

Whilst the current authors could find no indications of contemporary Iranian toxin or bioregulator research associated with incapacitating chemical agents (ICA)/CNS-acting chemicals, scientists at the Imam Hossein University (IHU) have previously conducted dual-use research into pharmaceutical chemicals that could be employed as such agents. This included work described in papers from 2007 till 2013, exploring the structural-activity relationships of fentanyl and its analogues, and attempts to generate stable long-lasting aerosols of medetomidine and other potential ICAs/CNS-acting agents.[60] In previous correspondence with the authors concerning this research, the Iranian CWC National Authority stated that the lead researcher was "interested in advance [of] academic and scientific chemical issues that [are] not prohibited by the Chemical Weapons Convention" and that the "academic research is financed by [the] ministry of science and technology and is "solely [for] scientific purposes".[61]

[57] Amnesty International (2020), *Iran: Scores injured as security forces use unlawful force to crush protests*, 15 January 2020; Amnesty International (2020), *Trampling Humanity: Mass arrests, disappearances and torture since Iran's November 2019 protests*, MDE 13/2891/2020, 2020; Motamedi, M. (2022), *Blame game after Iran women pepper-sprayed at World Cup qualifier,* Al Jazeera, 30 March 2022.

[58] US CWC Compliance Report (2020) op. cit., p. 10; US CWC Compliance Report (2021) op. cit. p. 14; US (April 2022) op. cit. p. 13.

[59] US CWC Compliance Report (2020) op. cit., pp. 10–11; US CWC Compliance Report (2021) op. cit. p. 14; US CWC Compliance Report (2022) op. cit. pp. 13–14.

[60] Crowley, M. and Dando, M. R. (2014) op. cit. pp. 34–38.

[61] Correspondence to Dr M,. Crowley, BNLWRP, from Dr H. Farajvand, Secretary of the National Authority for the CWC, Ministry of Foreign Affairs of the Islamic Republic of Iran, 15th July 2014, cited in Crowley, M. and Dando, M. R. (2014) op. cit. p. 37.

In its *2019–2022 CWC Compliance Reports*, the US stated that in 2014, the IHU chemistry department sought "kilogram quantities of medetomidine—*a sedative it has researched as an incapacitant*—from Chinese exporters" [emphasis added].[62] According to the US, the IHU chemistry department has "little history of veterinary or even medical research", and the quantities sought (over 10,000 effective doses) were "inconsistent with the reported end use of research".[63]

On 3 December 2020, the US introduced sanctions against SMG and its director, under Executive Order 13382 [Blocking Property of Weapons of Mass Destruction Proliferators and Their Supporters].[64] The US accused SMG of responsibility for projects "involving the testing and production of chemical agents for use as so-called incapacitation agents."[65] The US further highlighted that it was "concerned about the regime's true intent with regard to the testing and production of these so-called chemical incapacitation agents, which could be used either to further oppress Iranian citizens or for offensive purposes".[66]

On 1 December 2021, the 26th Conference of States Parties to the CWC [CSP-26] adopted a Decision to effectively outlaw the aerosolised use of CNS-acting chemical agents for law enforcement purposes.[67] Although 85 countries supported the Decision, Iran was among 10 States that voted against it. Just prior to the Decision's adoption, on 29 November 2021, Iran together with China, Russia and Syria declared that this Decision would be "an *ultra vires* act" which "could not have any legal effect(s) on the States Parties' rights and obligations under the

[62] US CWC Compliance Report (2019) op. cit. p. 9; US CWC Compliance Report (2020) op. cit. p. 12; US CWC Compliance Report (2021) op. cit. p. 115; US CWC Compliance Report 2022) op. cit. p. 16.

[63] Ibid.

[64] US CWC Compliance Report (*April* 2021) op. cit. p. 16; US CWC Compliance Report (2022) op. cit. p. 15. See also: Bush, G. (2005) US Executive Order 13382, Blocking Property of Weapons of Mass Destruction Proliferators and Their Supporters, 28 June 2005.

[65] US (2020) Sanctions on Iranian Entities Involved in Chemical Weapons Activities of Concern, press statement, US Department of State, 3 December 2020.

[66] Ibid.

[67] CWC (2021) *Decision: Understanding regarding the aerosolised use of central nervous system-acting-chemicals for law enforcement purposes.* C-26/DEC.10. Conference of States Parties, 26th Session. Organisation for the Prohibition of Chemical Weapons, The Hague.

Convention."[68] It is currently unclear whether Iran will accept the CSP-26 Decision and will implement it fully, including with regard to aerosolised bioregulator or toxin CNS weapons.

5.5 CWC Article X Declarations and the BTWC Confidence-Building Measures

Under both the BTWC and the CWC, States Parties are permitted to conduct research and associated activities including the production of appropriate quantities of potential weapons agents for "prophylactic, protection and other purposes" under the BTWC, and for "protective purposes" under the CWC. Recognising the danger that such activities could mask weapons programmes, both the OPCW and the BTWC States Parties have introduced relevant reporting and transparency mechanisms. Consequently, CWC States Parties are required under Article X of the Convention to provide annual declarations to the OPCW Technical Secretariat on "national programmes related to protective purposes", there is no requirement to make this information public, and Iran has not done so.[69]

Similarly, to enhance transparency, BTWC States Parties agreed to submit annual confidence-building measure (CBM) reports from 1987 to the States Parties/ISU on relevant national activities. According to the UNOG/ISU database, for the first ten years, Iran submitted no CBMs and subsequently its submissions have been irregular, with the last three Iranian CBM reports submitted in 2011, 2016, and 2021. Unfortunately, Iran has not made its CBMs publicly available.[70]

Consequently, it is not possible for civil society to directly establish whether Iran has reported to either the OPCW or BTWC States Parties/ISU on toxin and bioregulator research and other related activities undertaken or facilitated by defence establishments, and if so, whether it has identified them as being for protective or other permitted purposes. Some

[68] Iran (2021) *Joint Statement on behalf of 4 Delegations*. Delivered by the Delegation of the Islamic Republic of Iran at the 26th Session of the Conference of States Parties of the OPCW under the Subitem 26.1 "Any Other Business" on the Draft Decision entitled "Understanding Regarding the Aerosolized Use of Central Nervous System-Acting Chemicals for Law Enforcement Purposes". OPCW, The Hague, 29 November.

[69] OPCW, *CWC* (1993) op. cit., Article X, paragraph 4.

[70] United Nations, *Confidence Building Measures, Iran (Islamic Republic of)*, https://bwc-ecbm.unog.ch/state/iran-islamic-republic (accessed 22 April 2022).

information however can be obtained from the reports of other States and from civil society.

Leitenberg, who managed to obtain access to certain Iranian CBM submissions, reported that their 1998 and 1999 CBMs were incomplete: "they conveniently 'forgot' to submit perhaps the two most critical CBM…declarations…[i.e. those] list[ing] national biological defense research and development programs (Form A2) and past activities in offensive/defense biological research and development programs (Form F)."[71] According to Leitenberg, in 2002, Iran declared that it "did not and does not have any national, subnational or individual programs/activities and/or facilities related to biological offensive purposes" and that it "did not and does not have any 'National Biological Defensive Program'. However, the state has carried out some defensive studies on identification, decontamination, protection, and treatment against some agents and toxins."[72]

The US, which like all BTWC States, does have access to all CBM reports submitted to the ISU, has repeatedly raised concerns about the completeness of Iran's CBM reporting. According to the 2003 and 2005 US *Arms Control Compliance Reports*, Iran "failed to submit the data declarations called for in the BWC CBMs".[73] According to the 2019–2022 US *Arms Control Compliance Reports*, "prior to submission of an incomplete CBM in 2016, Iran had not submitted an annual CBM report since 2011." Like Leitenberg, the US noted Iran's statements that it "did not have a biodefense program", but "has carried out some defensive studies on identification, decontamination, protection, and treatment against some agents and toxins," adding that such statements were repeated in "previous Iranian CBM submissions."[74]

Following requests from the current authors for information on the toxin and bioregulator research and associated activities highlighted in this case study, on 3 June 2022, the Permanent Mission of the Islamic Republic of Iran to the United Nations Office and other International Organizations in Geneva stated: "It should be emphasized that the content of your

[71] Iranian CBM Submission to the BTWC, 2002, as quoted in Leitenberg, M. (2005) op. cit. p. 14.

[72] Iranian CBM Submission to the BTWC, 2002, as cited by Leitenberg, M (2005) op. cit. p. 15.

[73] United States Arms Control Compliance Report (2005) op. cit.

[74] United States Arms Control Compliance Report (2019) op. cit. p. 46; United States Arms Control Compliance Report (2020) op. cit. p. 57; United States Arms Control Compliance Report (2021) op. cit. p. 48; United States Arms Control Compliance Report (2022) op. cit. p. 36.

article is not substantiated. Having comments on the several allegations raised in your article requires more time. Generally speaking, Iran as a victim of the WMD that was used by Iraq in the 1980s, with the accomplice of the U.S. and some European countries, believes that the only guarantee against the use or threat of use of WMD is their total elimination."[75] Despite subsequent requests, no further substantive information has been forthcoming.

5.6 Concluding Remarks

While Iran has repeatedly stated that it rejects weapons of mass destruction, some past statements by Iranian officials appeared to contradict that position, and certain States have alleged that Iran did have, and/or may have, a biological weapons programme. Open-source information indicates a range of contemporary toxin and bioregulator research of potential dual-use application has been carried out, including by Iranian military-related institutions and researchers. Whilst at least certain such research has clear medical or protective applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied. Although Iran has submitted CBM reports to the ISU/BTWC States Parties, such reporting has been infrequent, and its veracity has been questioned by at least one State Party. It is unknown whether Iran has submitted Article X reports to the OPCW. Civil society does not have access to these BTWC and CWC reports as Iran has not published them in the open literature. In combination then these indicators suggest that there remains considerable distrust, in certain quarters, about Iran's dual-use toxin and bioregulator research activities.

It would be beneficial if Iran specifically addressed concerns about its previous and contemporary dual-use toxin and bioregulator research and associated activities through the BTWC CBM annual reporting process and its annual CWC Article X declaration. Furthermore, to increase public confidence in this area, it would be beneficial if Iran published unredacted version of such reports.

At least one Iranian company reportedly developed 'wide area' means of delivery potentially capable of disseminating RCAs, including OC or

[75] Iran (2022) Permanent Mission of the Islamic Republic of Iran to the United Nations Office and other International Organizations in Geneva, response to an information request from the University of Bradford, 3 June 2022.

PAVA, over large areas. Iran should provide details of which, if any, Iranian military, security, or police forces acquired such means of delivery, and if so provide details of any existing stockpiles, and the circumstances under which such means of delivery would be employed.

Iranian scientists have conducted research into pharmaceutical chemicals that could have dual-use application in relation to ICA/CNS-acting agents. In December 2021 Iran voted against the Decision adopted by CSP 26 prohibiting law enforcement use of aerosolised CNS-acting chemicals and questioned whether this Decision was legitimate. Consequently, it would be beneficial if Iran clarified whether it now accepted this Decision and would implement it fully, including with regard to aerosolised bioregulator or toxin CNS weapons.

Those States that have made public allegations about Iran's previous and contemporary dual-use toxin and bioregulator research and associated activities should employ the relevant consultation and/or investigation and fact-finding mechanisms under the CWC and BTWC, as appropriate, to raise and resolve their concerns.

CHAPTER 6

The Russian Federation Case Study

6.1 Overview of the Soviet Biological and Toxin Weapon Programme

The Soviet Union acceded to the Geneva Protocol in 1952; it signed the Biological and Toxin Weapons Convention (BTWC) in 1972 and ratified the Convention in 1984. However despite its obligations under the BTWC, the Soviet Union continued a biological weapons development programme which had been initiated in the 1930s.[1] It has been widely reported that in addition to five military biological weapons facilities under the control of the Ministry of Defence, a complex of nearly 50 scientific institutes and production facilities worked on biological weapons under the cover of the Soviet Academy of Sciences, the Ministry of Agriculture,

[1] United States (2020) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, June, p. 60; United States (2021) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments.* State Department, April, p. 50; United States (2022) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*, State Department. April, p. 38.

Following an information request by the authors, on 20 October 2021, the Russian Federation Government provided information on issues covered by the case study. Relevant extracts of this response are incorporated in the case study and a copy of Russia's response in full is contained in an Appendix of this publication.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_6

the Ministry of Health, and an ostensibly civilian pharmaceutical complex known as Biopreparat. This non-military biological weapons complex included major research and development centres in Moscow, Leningrad, Obolensk, and Koltsovo (Siberia) and standby production facilities in Omutninsk, Pokrov, Berdsk, Penza, Kurgan, and Stepnogorsk (Kazakhstan). Although numbers are contested, it has been claimed that approximately 70,000 scientists and technicians were employed in the Soviet biological weapons programme.[2] This biological weapons complex developed a broad range of biological pathogens for use against plants, animals, and humans[3] and explored weaponisation of certain toxins and bioregulators.[4]

Despite the industrial scale of its operations, for many years, the Soviet programme managed to completely hide or else disguise its work as legitimate civilian activities. In 1979 concerns about possible Soviet biological weapons activities grew and limited information emerged following the accidental release of aerosolised anthrax spores from Sverdlovsk Military Compound 19, killing over 60 people in the nearby closed city. Although Soviet authorities claimed the deaths were caused by tainted meat, Soviet military development was confirmed as the cause by Russian President Yeltsin in 1992.[5] Further detailed evidence of the nature and scale of the Soviet biological and toxin weapon programme was subsequently provided by scientists who had worked within this programme and later defected to the UK or US from 1989 onwards. Of particular note are the testimonies of Vladimir Pasechnik, the former general director of Science Production Organisation, Farmpribor, and director of the all Union Scientific Research Institute of Ultra Pure Biopreparations; Dr Kenneth Alibek (previously known as Kanatjan Alibekov) former Deputy Director for Science of Biopreparat; and Dr Sergei Popov, who worked at Vector and the Obolensk centre. Due to continued Russian secrecy, publicly available information concerning the Soviet biological and toxin weapons programme remains incomplete and many of the allegations unverified.

[2] Tucker, J. (1999) Bioweapons from Russia: Stemming the Flow. *Issues in Science and Technology*, **XV**(3), Spring.

[3] United States (2020) op. cit. p. 60; United States (2021) op. cit. p. 50; United States (2022) op. cit. p. 39.

[4] Alibek, K. and Handelman, S. (1999) *Biohazard: 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.

[5] United States (2020) op. cit. p. 60; United States, (2021) op. cit. p. 50; United States, (2021) op. cit. p. 39.

6.2 Soviet Toxin Weapon Research and Development

Soviet whistleblowing scientists have highlighted a number of projects—notably Project Bonfire, Project Factor and Project Flute—and identified individual facilities, where malign toxin and bioregulator research and development was undertaken. According to Alibek, the 15th Directorate of the Ministry of Health, which was responsible for biological weapons production facilities, controlled the Kirov Institute of Microbiology which "studied toxin weapons" and also the Sverdlovsk Institute of Military Technical Problems which undertook research into "toxic weapons, including botulinum toxin."[6] Furthermore, according to Alibek, the Third Main Directorate of the Ministry of Health established a network of laboratories under Project Flute that investigated biological agents that could "cause nonlethal and lethal organic and physiological changes" which included several labs that developed toxins and other substances for use against "individual human targets."[7]

Soviet scientists produced small-scale toxin weapons, subsequently employed as assassination weapons by at least one Warsaw Pact intelligence agency. In June 1978 Vladimir Kostov a Bulgarian dissident living in Paris, France, was attacked by a Bulgarian KGB operative employing an air gun-type delivery mechanism which implanted a minute metal pellet containing ricin into his body. During his 12-day hospitalisation, the pellet was discovered and ricin antibodies were detected; Kostov subsequently recovered. In September 1978 Georgi Markov, a Bulgarian dissident living in London, UK, was killed by a Bulgarian KGB operative using a delivery device hidden in an umbrella to inject a metal pellet again apparently containing ricin.[8] Alibek subsequently stated that the ricin for these attacks was developed by the Soviet Union's Laboratory 12, which "specialized in substances that could kill quickly, quietly, and efficiently". According to Alibek, "a special consignment of ricin [was] sent from Laboratory 12 to Sofia [and] KGB technicians were sent along to train Bulgarian agents."[9]

[6] Alibek, K.and Handelman, S. (1999) op. cit. pp. 297–298. It should be noted that these Soviet research and development activities are also described as "programs" rather than "projects" i.e. Program Bonfire, Program Factor and Program Flute.

[7] Alibek, K. and Handelman, S. (1999) op. cit. p. 302.

[8] Rozsa, L and Nixdorff, K. (2006) Biological Weapons in Non-Soviet Warsaw Pact Countries, pp. 157–168 in M. Wheelis et al. (Eds.), *Deadly Cultures, Biological Weapons Since 1945*. Harvard University Press, Harvard.

[9] Alibek, K. and Handelman, S. (1999) op. cit. pp. 173–174.

There have also been allegations by certain States, notably the US, of the development of toxin weapons subsequently employed in armed conflict. In the late 1970s and during the 1980s, the US alleged that Soviet-backed Laotian and Vietnamese armed forces had used 'yellow rain' toxin weapons against Hmong villages in Thailand resulting in casualties and deaths. The US stated that the "trichothecene toxins [used as weapons] were developed in the Soviet Union".[10] These allegations were questioned at the time including by academic civil society scientists notably Prof Matthew Meselson who argued that the substance "the Hmong had frequently mistaken as poison from the sky and which [the US Government] asserted was a chemical warfare agent, was, in fact, the faeces of Asian honey bees."[11] Although the US continued its allegations, the issue has remained formally unresolved.

6.3 Soviet Bioregulator Weapon Research and Development

According to Alibek, in addition to its 'classic' toxin weapons programme, Soviet scientists under Biopreparat's Project Bonfire also undertook research which was "intended to develop a new kind of toxin weapon"[12] based on bioregulatory peptides that "could damage the nervous system, alter moods, trigger psychological changes, and even kill".[13] From 1978, Project "Bonfire" scientists attempted to incorporate short DNA sequences that coded for the production of bioactive peptides into the genomes of bacteria and viruses. Their aim was to create genetically engineered microbes that would manufacture toxic substances and cause serious illness and death.[14] To the Soviet authorities, bioregulator weapons had a number of perceived benefits. Firstly, at least parts of an offensive development programme could be hidden in plain sight amidst dual-use biotechnology, pharmaceutical, and medical research. Secondly, as bioregulators

[10] Director of Central Intelligence (1982) *Use of Toxins and Other Lethal Chemicals in Southeast Asia and Afghanistan*. Special National Intelligence Estimate, 11/50/37–82, Vol 2. 26 February.

[11] Meselson, M. and Robinson, J.P. (2008) The Yellow Rain Affair: lessons from a discredited allegation, in Clunan, A. Lavoy, P, and Martin, S. (Eds.) *Terrorism, War, or Disease? Unravelling the Use of Biological Weapons*. Stanford University Press, Stanford. pp. 72–96.

[12] Alibek, K. and Handelman, S. (1999) op. cit. p. 154.

[13] Alibek, K. and Handelman, S. (1999) op. cit. p. 164.

[14] Alibek, K. and Handelman, S. (1999) op. cit. pp. 154–155.

are manufactured and are ubiquitous in the human body, the identification and effective treatment of bioregulator weapon use would prove difficult. Thirdly, the Soviet authorities falsely believed, or at least argued, that bioregulator weapons "based on compounds produced in the human body were not prohibited by the Biological Weapons Convention".[15] This is clearly an incorrect interpretation of the BTWC which under Article 1 explicitly prohibits weaponisation of all "microbial or other biological agents, or toxins". The current authors have requested that the Russian Federation clarify whether this incorrect Soviet interpretation of the BTWC with regard to development of bioregulator weapons was formally rejected by Russia, and to detail its current interpretation of the BTWC in this area. To date, no clarification of these specific matters has been received.

One area of investigation under Project Bonfire and Project Factor concerned the application of then-advanced genetic engineering techniques to the identification, investigation, and subsequent manipulation of the gene encoding myelin basic protein (MBP). According to Popov and Alibek, molecular biologists at the Soviet Academy of Sciences examined the properties of the naturally occurring MBP which maintains the correct structure of the body's myelin and is thought to be important in the process or myelination, that is coating the nerve fibres of the CNS with myelin sheaths, and thereby insulating and protecting them. Although essential to the normal functioning of the CNS, MBP when present in excessive amounts triggers an autoimmune reaction that damages the myelin sheaths and impedes the transmission of nerve impulses. This research was subsequently taken up by scientists at the State Research Center for Applied Microbiology in Obolensk, who inserted the gene for MBP into the bacterium *Yersinia pseudotuberculosis*. When guinea pigs were subsequently infected with the engineered bacteria, the microbes multiplied in the host releasing MBP and triggering an autoimmune reaction that caused death by paralysis in about two weeks.[16] According to Alibek, these results were considered a breakthrough: "[A] new class of weapons had been found.

[15] Alibek, K. and Handelman, S. (1999) op. cit. p. 155; see also Interview: Sergei Popov, *Journal of Homeland Security*, November 1, 2000 (updated November 19, 2002). Available at https://web.archive.org/web/20110719234905/www.homelandsecurity.org/journal/interviews/popovinterview_001107.htm; Davis, C. (1999) Nuclear Blindness: An Overview of the Biological Weapons Programs of the Former Soviet Union and Iraq. *Emerging Infectious Diseases,* **5**(4), 510.

[16] Interview: Serguei P*opov* (2000) op. cit.; Alibek and Handelman (1999) op. cit. pp. 163–167.

For the first time, we would be capable of producing weapons based on chemical substances produced naturally by the human body. They could damage the nervous system, alter moods, trigger psychological changes, and even kill."[17] Soviet scientists subsequently successfully inserted the myelin DNA code into the plague causing bacterium, *Yersinia pestis*. Fortunately, a toxin-plague weapon was never produced before the Soviet Union collapsed. However, these developments stimulated further research on bacteria-toxin combinations, with scientists studying the feasibility of inserting botulinum toxin genes into bacteria. Once again it appears no Soviet chimeric botulinum weapon was successfully developed.[18]

In other bioregulator research, conducted under Project Factor, Soviet scientists at the State Research Center for Virology and Biotechnology (Vector) near Novosibirsk engineered viruses by inserting genes coding for neuroactive peptides that affected brain function. Some of these experiments involved opiate-like neurotransmitters called enkephalins and endorphins, which in high concentrations can induce neurological and psychiatric disorders.[19] Popov, who worked at Vector from 1976 to 1986 and then at the Obolensk centre until 1992, stated that Vector had worked on endorphins, enkephalins, and other neuromodulating peptides potentially capable of altering human cognition and emotions. According to Popov, "[I]t has been discovered that personalities could be adjusted with these agents. For example, you could make people more aggressive. Or you could create feelings of insomnia, where people wanted to sleep, but would never feel tired."[20]

The Third Directorate of the Ministry of Health, under Project Flute, was also active in this area, with a network of biomedical research facilities that developed toxins, bioregulators, and other substances for use against individual human targets.[21] According to Alibek, this network included the Moscow Institute of Applied Molecular Biology (which later became the Russian Scientific Center of Molecular Diagnostics and Treatment)

[17] Alibek, K. and Handelman, S. (1999) op. cit. p. 164.

[18] Alibek,K. and Handelman, S. (1999) op. cit. pp. 166–167.

[19] Gilsdorf, J. and Zilinskas, R. (2005) New Considerations in Infectious Disease Outbreaks: The Threat of Genetically Modified Microbes. *Clinical Infectious Diseases*, **40**(8), 1 and 1160–1165.

[20] Interview: Sergei Popov (2000) op. cit. p. 11.

[21] Alibek, K. and Handelman, S. (1999) op. cit. pp. 171–172 and p. 302; See also Birstein, V. J. (2001) *The Perversion of Knowledge: The True Story of Soviet Science*. Westview Press, Boulder, Colorado. p. 107.

which studied "various biological substances in order to find those that could kill or cause irreversible mental damage" and the Moscow Institute of Immunology which studied "regulatory peptides with toxic properties capable of triggering both reversible and irreversible changes in the neural and immune systems."[22] In addition, the Moscow Scientific and Production Center of Medical Biotechnology undertook "basic research into human genome, in order to identify new BW possibilities" and the Moscow Region Center of Toxicology and Hygienic Regulation of Biopreparations studied "toxic biological compounds with a high killing potential for aerosol use."[23]

According to Alibek, "[T]he mood-altering possibilities of regulatory peptides were of particular interest to the KGB", possibly for use in coercion or interrogation of prisoners. In addition, the KGB were also interested in their application for covert assassination operations as such bioregulator weapons could not be traced by pathologists and victims would appear to have died of natural causes. "[W]hat intelligence service would not be interested in a product capable of killing without a trace?"[24] However, whilst whistleblower testimony has described Soviet bioregulator research and attempted development activities, there is no publicly available evidence that bioregulator weapons were produced or employed for interrogation, covert assassination operations or in armed conflict.

6.4 Termination of Soviet Biological and Chemical Weapons Programmes

In April 1992, the Russian President Boris Yeltsin signed a decree committing Russia, as the Soviet Union's successor, to fulfil its BTWC obligations and to end all illegal biological warfare activity in its territory. During discussions with US officials in Moscow in September 1992, Russian officials reportedly confirmed the existence of a biological weapons programme inherited from the Soviet Union and committed Russia to its

[22] Alibek, K. and Handelman, S. (1999) op. cit. p. 302.
[23] Alibek, K. and Handelman, S. (1999) op. cit. p. 302.
[24] Alibek, K. and Handelman, S. (1999) op. cit. p. 164.

destruction.[25] On 14 September 1992, at a news conference, Russian Deputy Foreign Minister Grigory Berdennikov revealed that:

> The Soviet Union was violating this convention [BTWC] and was running a program in the sphere of offensive biological research and development, which has been declared unlawful by the convention…. These activities were in progress from 1946 until March of 1992.[26]

During this period, the Yeltsin administration also terminated the Soviet chemical weapons programme and initiated measures to address its legacy, with Russia signing the Chemical Weapons Convention (CWC) in 1993 and ratifying the Convention in 1997. Russia formally declared possessing an arsenal of 39,967 metric tons of chemical agents, comprising lewisite, mustard, mustard-lewisite mixture, phosgene, sarin, soman, and VX.[27] It subsequently undertook a decades-long process to dismantle its declared chemical weapons production facilities (CWPFs) and destroy all its declared chemical weapons stockpiles. This process, which was undertaken under OPCW verification, was completed on 27 September 2017.[28] Full details of Russia's declared chemical weapons production facilities and declared stockpiles have not been made public. Consequently, it is not known whether Russia formally declared and subsequently destroyed any toxin or bioregulator production facilities or stockpiles, as part of this OPCW process.

From the early 1990s, the US worked with Russia—notably through the Nunn-Lugar Cooperative Threat Reduction (CTR) program—to

[25] United States (2022) op. cit. p. 39; United States (2021) op. cit. p. 50; see also Viktor Litovkin, "Yeltsin Bans Work on Bacteriological Weapons. This Means: Work Was Under Way, and We Were Deceived" [in Russian], *Izvestiya*, April 27, 1992, as cited in Zilinskas, R. (2016) *The Soviet Biological Weapons Program and Its Legacy in Today's Russia*. Center for the Study of Weapons of Mass Destruction, Occasional Paper, No. 11. National Defense University Press, July. footnote 131, pp. 44.

[26] Dahlburg, J. (1992) Russia Admits It Violated Pact on Biological Warfare. *Los Angeles Times*, 15 September 1992.

[27] See: *The Chemical Weapons Convention (CWC) at a Glance*, Arms Control Association, Last Reviewed: April 2020, https://www.armscontrol.org/factsheets/cwcglance; Sanders-Zakre, A. (2017) Russia Destroys Last Chemical Weapons. *Arms Control Today*, November, https://www.armscontrol.org/act/2017-11/news/russia-destroys-last-chemical-weapons; National Threat Initiative, *Russia, Chemical*, https://www.nti.org/learn/countries/russia/chemical/ (accessed 6 July 2021).

[28] Sanders-Zakre, A. (2017) op. cit.

dismantle or repurpose the Soviet biological and chemical weapons facilities and find employment for former biological and chemical weapons scientists and technicians in civilian biotechnological and chemical fields. Consequently, much of the direct threat and the associated dangers of proliferation from the former Soviet biological and chemical weapons programmes were subsequently eliminated.

6.5 Russian Biological and Toxin Research and Development Capabilities

Despite these significant advances, there have been long-running concerns voiced by States, notably the US, and academic researchers about the continued failures of Russia to provide full details of the former Soviet biological and toxin weapons programme and concerns that Russia conducted subsequent biological weapons related research and possibly biological weapons development activities. Such concerns were heighted following Vladimir Putin's assumption of the Presidency in 1999, and his subsequent rescinding of President Yeltsin's 1992 admission of the Soviet Union's illegal biological weapons activities. Subsequently, Russia's official position has been that the Soviet Union never had an offensive bioweapons programme and had only conducted defensive research as permitted under the BTWC.[29]

In its 2002 and 2003 reports under the *Cooperative Threat Reduction Act and the Freedom Support Act* (FSA), the US concluded that:

> Russia continues an offensive BW program, although it is much smaller than the massive Soviet BW program. Research activities with potential offensive applications are ongoing at certain facilities known to have been involved in offensive BW work during the Soviet era. Some civilian facilities previously associated with the Soviet offensive BW program have been subject to varying degrees of modification and equipment removal, and U.S. assistance has facilitated access to some of these civilian facilities, although many retain a capability to engage in offensive activity. Many key officials from the former Soviet offensive BW program continue to occupy influential positions. Funding for possible offensive BW activities at certain military sites has

[29] Zilinskas, R. (2016) op. cit. pp. 44.

> continued. Because the Ministry of Defense facilities remain closed to the West, the nature of Russian activities there remains uncertain.[30]

In 2004, in testimony before the US Senate Committee on Armed Services Subcommittee on Emerging Threats and Capabilities, Lisa Bronson, Deputy Under Secretary of Defence for Technology Security Policy and Counterproliferation, estimated that approximately 40 institutes that were formerly part of the Soviet BW programme still existed.[31]

In 2006 SIPRI researcher, Hart noted that:

> Concerns persist about a continued lack of responsiveness by Russian officials to requests by other governments for clarification regarding the fate of the former Soviet [biological and toxin weapons] program, the fact that a number of high-level officials in the current Russian CBW defense establishment are known or suspected to have been part of the Soviet BW program, and the fact that outside access to several Soviet BW military R&D facilities has never been allowed.[32]

In 2014, in testimony before the US House Committee, Dr Christopher Davis former principal biological warfare analyst at the UK's Defence Intelligence Staff contended that "[R]ussia did not admit to the real size and capability of its biological weapons systems and it did not get rid of all of them and did not allow the U.S. or the U.K. free unfettered access to its web of military as well as civilian BW sites." Dr Davis highlighted a wide range of unanswered questions that needed to be resolved, notably asking: "[W]hat happened to the bioregulator program?"[33]

[30] As cited in United States (2005), *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. U.S. Department of State, August.

[31] Bronson, L. (2004) *Cooperative threat reduction program*. Testimony of Lisa Bronson, Deputy Under Secretary of Defence for Technology Security Policy and Counterproliferation before the Senate Committee on Armed Services Subcommittee on Emerging Threats and Capabilities, 10 March.

[32] Hart, J. (2006) The Soviet Biological Weapons Programme, pp. 132–156 in M. Wheelis et al. (Eds.) *Deadly Cultures: Biological Weapons Since 1945*. Harvard University Press, Harvard. pp. 154–155.

[33] Davis, C. (2014) *Assessing the biological weapons threat: Russia and beyond*. Hearing before the Subcommittee on Europe, Eurasia and Emerging Threats of the Committee of Foreign Affairs, House of Representatives, 7 May.

Longstanding concerns about Russian capabilities and intentions with regard to possible development of biological and toxin weapons were further raised following the February 2012 publication of a lengthy article in the Moscow newspaper *Rossiiskaya Gazeta* by the then prime minister Putin, who was seeking election for the second time as President. Entitled "A Smart Defense against New Threats", the article detailed 28 tasks that a future Putin administration would address, and stated that:

> In the more distant future, weapon systems based on new principles (beam, geophysical, wave, *genetic*, psychophysical and other technology) will be developed. … All this will … provide entirely new instruments for achieving political and strategic goals. Such high-tech weapon systems will be comparable in effect to nuclear weapons but will be more 'acceptable' in terms of political and military ideology. (Emphasis added)[34]

According to Zilinkas, on 22 March 2012, following his election, President Putin chaired a meeting at which his ministers described how they would implement the 28 tasks Putin had detailed in his *Rossiiskaya Gazeta* article. Minister of Defense Anatoly Serdyukov stated, "[M]r. Putin, we have thoroughly studied your article and prepared a plan for implementing the tasks set there for the Defense Ministry."[35] According to Zilinkas, Serdyukov specifically promised to implement Task 4—to create weapons systems that use new principles.[36] By early April 2012, Putin's "Task #4" had been removed from the Russian government websites where it had previously been posted.[37] No further substantive information was made available by the Russian Government on the nature of such "genetic weapons" but such a broad term would potentially encompass weapons

[34] Original article [in Russian] was reprinted by the following source: Vladimir Putin, "Being Strong: National Security Guarantees for Russia," Rt.com, 20 February 2012. Available at http://rt.com/politics/official-word/strong-putin-military-russia-711/.

[35] Prime Minister Vladimir Putin Holds a Meeting on the Tasks He Set in His Articles as a Presidential Candidate. Transcript, March 22, 2012. *Archive of the Official Site of the 2008–2012 Prime Minister of the Russian Federation Vladimir Putin*, available at http://archive.premier.gov.ru/eng/events/news/18490.

[36] Zilinskas, R. A. (2016) op. cit. p. 45; see also Zilinkas, R. A. (2012) Take Russia to 'task' on bioweapons transparency. *Nature Medicine*, 18(6); Hoffman, D. (2012) Genetic Weapons, You Say? *Foreign Policy*, 27 March 2012; Leitenberg, M. (2021) False allegations of biological-weapons use from Putin's Russia. *The Nonproliferation Review*, 12 October 2021, DOI: 10.1080/10736700.2021.1964755.

[37] Zilinkas, R. A. (2012) op. cit.

utilising toxins or bioregulators or other malign manipulation of the body's bioregulatory processes. Furthermore, it is unclear and contested whether President's Putin's call was for the Russian development of "genetic weapons" or instead for Russia to respond to such weapons developed by other States.[38]

6.6 US Sanctions on Research Facilities Allegedly Linked to Russian BW Programmes

In the light of its long-running concerns about historic Soviet and contemporary Russian activities potentially related to biological weapons, on 27 August 2020, the US Department of Commerce added the 48th Central Scientific Research Institute, Kirov; 48th Central Scientific Research Institute, Sergiyev Posad; and 48th Central Scientific Research Institute, Yekaterinburg to its *Entity List* under the US Export Administrative Regulations "of persons and organizations" found to be engaged in "activities contrary to [U.S.] national security and/or foreign policy interests".[39] The US stated it had "reasonable cause to believe these institutes are Russian Ministry of Defense facilities associated with the Soviet and Russian biological weapons program."[40] On 18 November 2020, Dr Christopher Ashley Ford, US Assistant Secretary of State for International Security and Nonproliferation, further clarified the US position:

> [T]he spectre of state-sponsored biological warfare has never left us. In fact, in August of this year, the [US] announced measures to block commercial dealings with certain Russian government institutes involved in the Russian biological weapons program, thus *publicly and officially making clear for the*

[38] For further discussion see: Leitenberg, M. (2021) op. cit; NTI (2014), Russia Rejects Bioweapons Talk in U.S. Congress as 'Propaganda', 13 May 2014 .

[39] US Export Administration Regulations, Part 744, Supplement No. 4, see: US Federal Register (2020), *Addition of Entities to the Entity List, and Revision of Entries on the Entity List*, August 27, www.federalregister.gov/documents/2020/08/27/2020-18909/addition-of-entities-to-the-entity-list-and-revision-ofentries-on-the-entity-list; see also United States (2021) op. cit. p. 52; United States (2022) op. cit. p. 40.

[40] US Federal Register (2020) *Addition of Entities to the Entity List, and Revision of Entries on the Entity List*, August 27, www.federalregister.gov/documents/2020/08/27/2020-18909/addition-of-entities-to-the-entity-list-and-revision-ofentries-on-the-entity-list; see also United States (2021) April, op. cit. p. 52; United States (2022) op. cit. p. 40.

> *first time that there is still a Russian biological weapons program.* (Emphasis added)[41]

Subsequently in its 2021 and 2022 *Arms Control Compliance Reports*, the US declared that "the Russian Federation (Russia) *maintains an offensive BW program* and is in violation of its obligation under Articles I and II of the BWC" (emphasis added).[42]

6.7 Contemporary Dual-Use Toxin Research[43]

There is clearly an active Russian civilian chemical and life science research community, conducting research on toxins, bioregulators, and bioregulatory systems, that does not appear to be directly connected with Russian military or other defence or security institutions, or to raise obvious dual-use concerns. This includes Russian involvement in a range of international biomedical and biotechnological toxin research projects, for example, investigating saxitoxin producing bacteria in Russian freshwaters,[44] and the biosynthesis of tetrodotoxin.[45]

[41] Global partnership against the spread of weapons and materials of mass destruction, plenary meeting (2020) *Our global partnership against chemical weapons abuses*: See remarks of Dr. Christopher Ashley Ford, Assistant Secretary, Bureau of International Security and Nonproliferation, November 12, 2020; both available at https://2017-2021.state.gov/our-global-partnership-against-chemical-weapons-abuses/index.html.

[42] United States *Arms Control Compliance Report* (2021) op. cit. p. 50; United States *Arms Control Compliance Report* (2022) op. cit. p. 38.

[43] Whilst this Section discusses contemporary dual use research, such activities have a long history. For example, in 1992 scientists at the State Scientific-Research Institute of Organic Chemistry and Technology (GosNIIOKhT) in Moscow published a paper on the synthesis of analogues of one of the most powerful known agents at causing chemotaxis, FMLP tripeptide. The two peptide analogues synthesised were injected into the tail veins of rats and shown to reduce their arterial blood pressure. The authors stated that: "It is clear that analogues of formyltripeptide having a milder hypotensive action, may be considered as potential medicinal preparations." However, given that such peptides are simple in structure and easily synthesised, the work could be viewed as potentially having dual-use application. See: V.V. Ryakhovskii, V. V. et al. (1992) Synthesis of chemotactic tripeptide analogs containing L- and D-(S-trifluoromethyl)-homocysteine and having hypotensive activity. *Khimiko Farmatsevticheskii Zhurnal*. **26**(2), 46–49.

[44] See for example, Chernova, E. et al. (2017) *Dolichospermum* and *Aphanizomenon* as neurotoxin producers in some Russian Freshwaters. *Toxicon*, **130**, 47–55. p. 53.

[45] Melnikova, D. I. et al. (2021) The First Data on the Complete Genome of a Tetrodotoxin-Producing Bacterium. *Toxins*, **13**, 410. https://doi.org/10.3390/toxins13060410. pp. 6–7.

However, there is continued concern with regard to the potential activities of certain Russian research facilities. For example, the US, in its 2019–2021 *Arms Control Compliance Reports*, claimed that "[R]ussian government entities remained engaged in dual-use activities during the reporting period, potentially for purposes incompatible with the BWC."[46] It is not known whether this statement refers to the three Russian government institutes that the US claimed were "involved in the Russian biological weapons program" and sanctioned in August 2020 or covers additional entities.

We take the general position that it is not for us to make judgements about the purpose of specific research with potential dual-use implications. However, it has to be acknowledged that work done by Russian researchers with decade-long careers in toxin research and located in civilian institutes with known previous connections with military-orientated BW-related research could give rise to potential dual-use concerns and/or possible misperceptions. An illustrative example where such dual-use concerns or misperceptions may arise relates to the Gamaleya Institute.

The Soviet biodefence programme was named Problem 5. It involved six "anti-plague" institutes and their subsidiary "anti-plague" stations and other institutions.[47] According to Zilinskas and Mauger, the Gamaleya Institute was the lead scientific establishment for this programme. They state: "[T]he Gamaleya Institute's classified R&D conducted under Problem 5 was focussed on bacteria, select unusual viruses, epidemiology, vaccine production, and diagnostics." In addition, they claim that "*[G]amaleya scientists also conducted offensive R&D for the Soviet BW program*"[48] (emphasis added).

Zilinskas and Mauger further contend that researchers at the Gamaleya Institute undertook biodefence-related research activities following the collapse of the Soviet Union, including those related to toxins:

> Recently, the Gamaleya Institute has also conducted toxin R&D. Since 2007, its scientists have developed immunoassays for identifying botulinum toxins and diagnostic products for identifying staphylococcal enterotoxin B

[46] United States *Arms Control Compliance Report* (2022) op. cit. p. 39; similar statements were made in United States *Arms Control Compliance Report* (2019) op. cit., p. 49; United States *Arms Control Compliance Report* (2020) op. cit. p. 62: United States *Arms Control Compliance Report* (2021) op. cit. p. 51.

[47] It should be noted that the term "anti-plague" in the Soviet biodefence programme was used broadly to indicate not only activities to combat the disease casued by Yersinia pestis , but also other dangerous endemic and exotic diseases caused by viruses and bacteria.

[48] Zilinskas, R. A. and Mauger, P (2018) *Biosecurity in Putin's Russia*. Lynne Rienner, Boulder. pp. 152–153.

> (SEB) toxin. Given these R&D efforts, the Gamaleya Institute clearly remains involved in Russia's biodefense efforts.[49]

It appears that potentially relevant research has subsequently continued. The website of the Gamaleya Institute describes its present work as follows:

> The main scope of its activities includes solving fundamental research challenges in epidemiology, medical and molecular microbiology, infectious disease immunology, and biotechnology. These studies focus specifically on the general and specific patterns inherent in the spread and epidemic manifestations of infectious diseases; the structure and dynamics of infectious disease pathology among the population; the occurrence, functioning, and epidemic manifestation of natural foci for human diseases; the genetics, molecular biology, environments, and persistence of pathogenic microorganisms; the problems involved in general and infectious disease immunology, including immunoregulation and immune system adjustment; the methods and equipment used in diagnostic work and preventing infectious diseases; developing technologies to analyze and forecast infections of the processes involved in the mass spread of diseases protect the Russian population of Russia; biotechnology; nanotechnology; developing technology platforms to create new-generation vaccines.

An example of such modern work by the institute is a 2019 report by five members of the Department of Genetics and Bacteria Molecular Biology, four members of the Department of Bacteriology, and two members of the Department of Medical Microbiology explaining their use of genetic engineering methods to modify monoclonal botulinum toxin antibodies. This research which extended the antibody half-life has clear medical utility.[50] Most of the authors of this paper have numerous related papers published during this century that are accessible though the Pub Med website. Interesting exceptions are three members of the Department of Bacteriology where the Pub Med database shows few papers by two of the authors published since 2000, but papers on botulinum neurotoxin published during the 1980s.[51] In addition the third author who has more publications during this century, including one with members of the

[49] Zilinskas, R. A. and Mauger, P. (2018) op. cit. p. 153.

[50] Godakova, S. A. et al. (2019) Camelid VHHs Fused to Human Fc Fragments Provide Long Term Protection Against Botulinum Neurotoxin in Mice. *Toxins*, **11**, 464; doi:10.3390/toxins1180464.

[51] See for example, Vinogradova, I. D. et al. (1983) Preparation of neurotoxin and hemagglutinin for *Clostridium botulinum* A and characterization of its neurotoxin. *Biokhimila*, **48**(5), 788–796; Vinogradaova, I. D. et al. (1984) Characterization of the subunits of botulinum neurotoxin type A. *Biokhimlia*, **49**(3), 426–431.

Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry,[52] again published papers on staphylococcal enterotoxins during the 1980s.[53] Work on botulinum toxin and SEB during that period of the 1980s when such toxins were being weaponised by States might well raise dual-use questions.

Similar dual-use concerns could arise from long-term work by researchers at the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry. A key scientific figure in the Soviet offensive biological weapons programme was Yuri Ovchinnikov after whom the Institute is partly named. As Birstein explained, Ovchinnikov[54] "[D]irected the huge Academy Institute of Bioorganic Chemistry and was a leading proponent of using molecular biology and genetic methods for creating new types of biological warfare." The Institute's website describes the main scope of its current work as follows:

> Currently, the Institute and its Branch consist of 18 scientific departments (more than 70 research laboratories) and employ more than 1300 people including 15 members of Russian Academy of Sciences, >700 scientific researchers (>80 D.Sc., ~300 Ph.D.,). About 400 scientific articles are published annually in international journals in the fields of physicochemical properties of peptides and proteins, nucleic acids and lipids, concerning the studies of the mechanisms of biological membranes functioning as well as the investigation of the structure and biological role of low-molecular-weight bioregulators (steroid hormones, antibiotics, etc.). A significant cycle of the Institute's work is devoted to practical aspects that are important for medicine, agriculture, and a number of industrial fields.

In line with Zininskas' and Mauger's opinion that this Institute is the country's top research centre for toxins, for example, one of its leading scientists has published over 200 research papers with the latest being in 2019 and the earliest in 1973 (this paper on the amino acid sequence of

[52] Rudenko, N. V. et al. (2018) Immunochemical assay with monoclonal antibodies for detection of staphylococcal enterotoxin H. *Journal of Food and Drug Analysis*, **26**, 741–750.

[53] Ezepchuk, Y. U and Noskov, A. N. (1985) NH_2-Terminal Localization of the Part of the Staphylococcal Enterotoxins Polypeptide Chain Responsible for Binding with Membrane Receptor and Mitogenic Effect. *Int. J. Biochem.*, **18**(5), 485–488.

[54] Birstein, V. J. (2001) *The Perversion of Knowledge: The True Story of Soviet Science*. Westview Press, Boulder. p. 414. See also "The Key Role of Ovchinnikov" pp. 18–25 in Zilinskas, R. A. (2016) op. cit.

cobra venom having Yu A. Ovchinnikov as one of the co-authors).[55] This scientist's research during their long career covers the range of work on toxins described in Sect. 2.3 of this current book from discovery of toxins in venoms of snakes, insects, and marine organisms, to the definition of their structure and function, through to their use to elucidate how they interact with receptors and affect the functions of living organisms. And, of course, this vast amount of work on toxins is being employed and further developed by other members of this Institute.[56]

In addition, we found scientists in other Russian institutions publishing research on toxins that could be of dual-use interest. For example, toxins secreted by poisonous frogs have been seen as having military potential,[57] and scientists at the Laboratory of High Technology, 86 Vernadsky Prospect in Moscow, published a paper on the synthesis of structural analogues of epibatidine in 2015.[58] Epibatidine is a toxin from the skin of an Ecuadorian frog and has been of considerable interest as its analgesic effect is caused by action on nicotinic acetylcholine receptors rather than on opioid receptors.[59]

We also found examples of scientists in military institutes working on toxins of potential dual-use concern. For example, in the rapidly advancing field of fungal toxin research,[60] scientists at the Kirov Military Medical

[55] Grishin, E. V. et al. (1973) Amino Acid Sequence of Neurotoxin from *Naja Naja Oxiana* Venom. *FEBS Letters*, **36**(1), 77–78.

[56] Kasheverov, I. E. et al. (2019) Scorpion toxins interact with nicotinic acetylcholine receptors. *FEBS Letter*, **593**, 2779–2789; Tsetlin, V. I., et al. (2020) Tree-finger proteins from snakes and humans acting on nicotinic receptors: Old and new. *Journal of Neurochemistry*. Doi: 10.1111/jnc.15123; Utkin, Y. N. (2017) Modern trends in animal venom research—omics and nanomaterials. *World Journal of Biological Chemistry*, **8**(1) 4–12; Utkin, Y. N. (2021) Animal Venoms and Their Components: Molecular Mechanisms of Action. *Toxins*, **2021**, 13, 415. https://doi.org/10.3390/toxins13060415.

[57] Zhang, X. et al. (2014) Military potential of biological toxins. *Journal of Applied Biomedicine*, **12**, 63–77. See pages 73–74 on Batrachotoxin.

[58] Babkin, I. Y. et al. (2015) Synthesis of structural analogues of epibatidine. *Russian Chemical Bulletin*, **64**(2). 466–469.

[59] Salehi, B. et al. (2019) Epibatidine: A Promising Natural Alkaloid in Health. *Biomolecules*, **9**(1): 6, Doi: 10.3390/biom9010006; see also, Semchenko, F. M. (2013) Preparative-Scale Production of the Analgesic (2R*)-2-(6'-Chloropyridin-3-YL)-7-Azabicyclo[2.2.1]Heptane (Epibatidine). Pharmaceutical Chemistry Journal, 47(8), 437–441.

[60] Landi, N. et al. (2022) An Updated Review of Bioactive Peptides from Mushrooms in a Well-Defined Molecular Weight Range. *Toxins*, **2022**, 14, 84. https://doi.org/10.3390/toxins14020084.

Academy and the State Scientific-Research Test Institute of Military Medicine in St Petersburg published a review paper in 2021, which investigated the 150 poisonous macromycetes (fungal species that produce large fruit bodies) found in Russia and described the different kinds of poisonous and hallucinogenic molecules that they produce and the molecular mechanisms by which some of these molecules cause their effects.[61] Similarly, scientists at Research Center 33 of the Central Research and Investigation Institute of the Ministry of Defense of Russian Federation in Moscow were amongst a group that published a paper on a rapid test for toxins from *Amanita phalloides* mushrooms in 2013.[62] More generally, we found scientists from the 27 Scientific Center of the Ministry of Defense of the Russian Federation in Moscow had published a paper on the use of advanced techniques for the identification and the quantitative determination of tetrodotoxin in 2017.[63]

The point here is not that any of this current dual-use work is necessarily being done for malign purposes. Indeed, much of it has important medical uses. However, without the introduction of effective transparency and confidence-building measures (CBMs) by Russia, it cannot be assumed that some other States will not harbour concerns about such sophisticated contemporary research being done by people and institutes that were previously involved in dual-use research during the last century at the time of the Soviet BW programme. Furthermore, as Zilinskas and Mauger argued, such concerns are not reduced given the uncertainty about Russian State policy on biotechnology at the present time.[64]

6.8 Russian Incapacitating Chemical Agent (ICA)/ Central Nervous System (CNS)–Acting Weapons

Information presented by academic researchers and those based in certain State CBW defence facilities have described work undertaken by Soviet scientists to develop CNS-acting chemical (also called incapacitating

[61] Khovpachev, A. A. et al. (2021) Actual Concepts of Higher Fungi's Toxins: Simple Nitrogen-Containing Compounds. *Biology Bulletin Reviews*, **11**(2), 198–212.

[62] Gulikova, D. K. et al. (2017) A Rapid Test for Toxins from *Amanita phalloides* Mushrooms. *Journal of Analytical Chemistry*, **68**(12), 10898–11092.

[63] Shalabai, V.V. et al. (2017) Use of High-Performance Liquid Chromatography Coupled with High-Resolution Mass Spectrometry for the Identification and Quantitative Determination of Tetrodotoxin in Pharmaceuticals. *Journal of Analytical Chemistry*, **72**(6), 632–638.

[64] Zilinskas, R.A. and Mauger, P. (2018) op.cit., Chap. 7: Policy Suggestions and Possible Future Collaborations, pp. 351–360.

chemical agent) weapons. Soviet research and development activities apparently concentrated upon certain classes of pharmaceutical chemicals with anaesthetic or analgesic properties, for example, carfentanil and fentanyl.[65] In addition, as highlighted in Sects. 6.2 and 6.3 of this case study, Soviet military scientists also attempted to develop toxin and bioregulator weapons intended to malignly manipulate or effect those targeted without resulting in serious long-term injury or death.

Following the collapse of the Soviet Union, the Russian Federation clearly maintained stockpiles of at least certain CNS-acting weapons and the capability to use them. In October 2002, Russian security forces used a CNS-acting chemical weapon against armed Chechen separatists holding 900 hostages in a Moscow theatre. Although the bulk of the hostages were freed, more than 120 died from the effects of the chemical agents, and an undermined but large number of additional hostages have suffered long-term damage or died prematurely in the years following the siege (Fig. 6.1).

Although Russia has to date refused to fully identify the CNS-acting chemicals employed, analysis by the UK's Defence Science and Technology Laboratory indicated that the weapon comprised two analgesic-anaesthetics, carfentanil and remifentanil.[66] Russian scientists have subsequently undertaken research potentially related to CNS-acting weapons.[67] This has included computer modelling of the employment of an aerosolised chemical "calmative" against groups of individuals in enclosed spaces[68] and exploration of potential CNS-acting chemical agent interaction with human opioid receptor sites.[69]

[65] Perry Robinson, J. (2012) "Incapacitating chemical agents" in context: an historical overview of states policy in: *Incapacitating chemical agents: Law enforcement, human rights law and policy perspectives*. Montreux, Switzerland, 24th–26th April, p. 92; Crowley, M. and Dando, M. R. (2014) op. cit., pp. 42–43.

[66] Riches, J. et al. (2012) Analysis of Clothing and Urine from Moscow Theatre Siege Casualties Reveals Carfentanil and Remifentanil Use', *Journal of Analytical Toxicology*, **36**(9), 647–656.

[67] For further discussion, see: Crowley, M. and Dando, M. R. (2014) op. cit., pp. 42–50.

[68] Klochikhin, V. et al. (2005) M. Principles of Modelling of the Scenario of Calmative Application in a Building with Deterred Hostages. *Proceedings of the 3rd European Symposium on Non-Lethal Weapons*, Ettlingen, Germany, 10–12th May 2005, V17, Pfinztal: Fraunhofer ICT.

[69] Kuzmina, N., Kuzmin, V. (2011) Development of concepts on the interaction of drugs with opioid receptors. *Russian Chemistry Reviews*, **80**, 145–169. For further examples see: Riches, J. et al. (2012) op. cit.; Crowley, M. and Dando, M. R. (2014) op. cit. p. 49.

Fig. 6.1 Russian President Vladimir Putin Visits Survivors from the Moscow Theatre Siege, October 2002. (Copyright Creative Commons)

In recent years, a growing group of CWC States Parties have advocated that the law enforcement use of aerosolised CNS-acting chemicals should be addressed by the OPCW. Russia has previously opposed such measures. In a November 2018 paper issued during the Fourth CWC Review Conference, Russia stated that use of aerosolised CNS-acting chemicals for law enforcement purposes "is not regulated under the [Chemical Weapons] Convention."[70]

On 11 March 2021, the OPCW Executive Council adopted a Decision that "[R]ecommend[ed] that the Conference at its Twenty-Sixth Session decide that the aerosolised use of CNS-acting chemicals is understood to be inconsistent with law enforcement purposes as a

[70] Russian Federation (2018) *Aerosolisation of Central Nervous System-Acting Chemicals for Law Enforcement Purposes*, RC-4/NAT.9, p. 3. OPCW, The Hague, 21 November.

'purpose not prohibited' under the Convention."[71] The Russian Federation voted against the OPCW Decision. The current authors requested clarification from the Russian Federation on its position on these issues and specifically whether it considers that the development, production, and use for law enforcement of aerosolised toxins, bioregulators, and other biologically active peptides should be prohibited under the CWC. In its 20 October 2021 response to the authors, the Russian government stated:

> Chemicals affecting the central nervous system (CNS-chemicals) are not covered by the CWC. Our position on this issue is laid out in detail in national documents EC-93/NAT.6 and EC-96/NAT.6.… The consultations among the CWC States Parties in OPCW since 2008 on the CNS-chemicals and its elaboration by OPCW Scientific Advisory Board (which is far from completion) have shown that this topic requires comprehensive research and examination rather than imposing by certain countries of their own interpretation of the Convention.[72]

This contrasts with the OPCW Scientific Advisory Board's (SAB) 2018 recommendation to the Fourth Review Conference of the CWC, which stated that:

> Technical discussions of so-called "incapacitating chemicals" or central nervous system-acting (CNS) chemicals remain exhausted. The SAB sees no value in revisiting this topic as scientific facts remain unchanged since the SAB first considered this issue. In view of the increasing availability of such chemicals, the Secretariat should be prepared to develop capabilities that could be required to conduct missions involving an alleged use of CNS-acting chemicals for hostile purposes, including sample collection and the addition of analytical data to the OPCW Central Analytical Database (CAD). This is consistent with previous advice on the subject.[73]

[71] OPCW (2021) *Executive Council, Decision: Understanding regarding the aerosolised use of central nervous system-acting chemicals for law enforcement purposes*, EC-96/DEC.7, 11 March.

[72] Russian Delegation to the UN Conference on Disarmament, response to an information request from the University of Bradford, 20 October 2021.

[73] OPCW (2018) *Report of the Scientific Advisory Board on developments in science and technology for the Fourth Review Conference*, RC-4/DG.1, 30 April, paragraph 27.

On 1 December 2021, the 26th Conference of States Parties to the CWC (CSP-26) adopted a landmark Decision to effectively outlaw the aerosolised use of CNS-acting chemical agents for law enforcement purposes. The Decision also noted that "munitions and devices specifically designed to cause death or other harm" through the release of aerosolised CNS-acting chemicals would "constitute a 'chemical weapon'",[74] and consequently should be declared and verifiably destroyed. Although 85 countries supported the Decision, Russia was among 10 States that voted against it. On 29 November 2021, Russia (together with China, Iran and Syria) issued a joint statement detailing its opposition to this Decision and declaring that:

> We consider the decision a clear departure from provisions of the Convention as it changes drastically the strike balance which exists between the rights and obligations of the States Parties under the Convention.… We do categorically reject the decision as adopted, we believe that the decision is not consistent with the provisions of the Convention as it compromises the rights of the States Parties under this instrument… we do consider the decision as an ultra vires act which goes beyond the powers and functions of the Policy-Making Organs of the OPCW, so could not have any legal effect(s) on the States Parties' rights and obligations under the Convention.[75]

6.9 Russian Riot Control Agent Delivery Mechanisms

Russian companies and State entities have researched and developed a range of riot control agent (RCA) means of delivery—including handheld sprayers which disseminate oleoresin capsicum (OC)—a sensory irritant of biological origin—in limited quantities and over relatively small areas. They are promoted for use by Russian law enforcement agencies

[74] OPCW (2021) *Decision: Understanding regarding the aerosolised use of central nervous system-acting-chemicals for law enforcement purposes.* CWC Conference of States Parties, 26th Session. C-26/DEC.10.

[75] OPCW (2021) *Joint Statement on behalf of 4 Delegations delivered by the Delegation of the Islamic Republic of Iran* at the 26th Session of the Conference of States Parties of the OPCW under the Subitem 26.1 "Any Other Business" on the Draft Decision entitled "Understanding Regarding the Aerosolized Use of Central Nervous System-Acting Chemicals for Law Enforcement Purposes", 29 November.

and also for export. If used in appropriate amounts and circumstances, they would appear to be consistent with the BTWC and CWC.[76]

In contrast, at least one Russian company reportedly developed a range of large calibre munitions and other devices intended to disseminate "irritant-action pyrotechnic composition" over wide areas or extended distances, some of which may be inconsistent with the CWC and potentially also the BTWC. According to the 2009 English language version of the 2006 *Ordnance and munitions* volume of *Russia's Arms and Technologies*, the 'wide area' RCA means of delivery included 30 mm grenade rounds for automatic launchers, 105 mm rocket-propelled grenades, 82 mm mortar shells weighing 3.5 kilograms and capable of reaching distances of more than 2.6 kilometres, 120 mm munitions weighing 16 kilograms for use in mortars or artillery that could reach up to 6.8 kilometres, munition dispensers carried by helicopters, and even 500-kilogram cluster bombs packed with chemical irritant submunitions designed to be dropped from low-altitude helicopters or aircraft flying up to 12,000 meters above the target. Information on these RCA means of delivery was last made publicly available in 2009.[77] It is not known whether production of these munitions and devices continues, or whether stocks remain.[78] Whilst the nature of the "irritant-action pyrotechnic composition" employed was not identified, these delivery mechanisms appear capable of employing a range of RCAs, and a number potentially could deliver or be adapted to deliver OC and its synthetic analogues.

[76] There have been reports of excessive or inappropriate use of unidentified 'limited area' OC means of delivery by Russian law enforcement officials. Such practice would appear to contravene relevant human rights law and standards. See for example: Amos, H. 'I Had to Breathe Through My Clothes': Russian Police Pepper-Sprayed Protesters in a Cell. *Moscow Times*, 23 June 2017; Human Rights Watch (2021) *Russia: Arbitrary Detentions at Pro-Navalny Protests*, 22 April.

[77] Non-lethal munitions section, Volume 12 "Ordnance and Munitions" (English language version), Russia's Arms and Technologies. *The XXI Century Encyclopedia*, (version 2006.1eng). Arms and Technologies Publishing House, 5th May 2009.

[78] Crowley, M. (2009) *Dangerous Ambiguities: Regulation of Riot Control Agents and Incapacitants under the Chemical Weapons Convention*. Bradford Non-lethal Weapons Research Project, October, pp. 108–110; Crowley, M. (2013) *Drawing the line: regulation of 'wide area' riot control agent delivery mechanisms under the Chemical Weapons Convention*, University of Bradford/Omega Research Foundation, April, pp. 25–38; Crowley, M. (2016) *Chemical Control: Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery*. Palgrave Macmillan, Basingstoke, 2016, pp. 99–104.

6.10 CWC Article X Declarations and the BTWC Confidence-Building Measures

Under both the BTWC and the CWC, States Parties are permitted to conduct research and associated activities including the production of appropriate quantities of potential weapons agents for "prophylactic, protection and other purposes" under the BTWC, and for "protective purposes" under the CWC. Recognising the danger that such activities could mask weapons programmes, both the OPCW and the BTWC States Parties have introduced relevant reporting and transparency mechanisms. Consequently, CWC States Parties are required under Article X of the Convention to provide annual declarations to the OPCW Technical Secretariat on "national programmes related to protective purposes". There is currently no requirement to make Article X declarations public, and the Russian Federation has not done so.[79] Similarly, to enhance transparency, BTWC States Parties agreed to submit annual confidence-building measure (CBM) reports from 1987 to the States Parties/ISU on relevant national activities. Since 1987, the Russian Federation has submitted CBMs to the BTWC States Parties/ISU on an annual basis, with the latest CBM submitted in 2022. However, none of these CBMs are publicly available.[80]

Consequently, it is not possible for civil society to directly establish whether the Russian Federation has reported to either the OPCW or BTWC States Parties/ISU on toxin and bioregulator research and other related activities undertaken or facilitated by defence establishments, and if so, whether it has identified them as being for protective or other permitted purposes. Some information however can be obtained from the reports of other States and from civil society.

The US, which like all BTWC States does have access to such reports, has repeatedly raised its significant concerns about Russia's CBM reporting. In its 2019 *Arms Control Compliance Report*, the US stated that: "[I]n its CBM submission of April 11, 1992, Russia acknowledged that the former Soviet Union had "[p]ast offensive programs of biological research and development" from 1946 to March 1992"; however, the US

[79] OPCW, *CWC* (1993) op. cit. Article X, paragraph 4.

[80] United Nations, *Confidence Building Measures, Russian Federation*, https://bwc-ecbm.unog.ch/state/russian-federation (accessed 25 April 2022).

claimed that Russia had "*fail*[ed] *to account for production, testing, and weaponization activities*" (emphasis added).[81]

In its 2020–2022 *Arms Control Compliance Reports*, the US stated that "[W]hile States Party to the BWC have a political commitment to report a past offensive program, since April 11, 1992, subsequent Russian CBM submissions have remained incomplete and misleading."[82] In its 2022 *Arms Control Compliance Report*, the US determined that:

> Russia has provided an incomplete acknowledgment of the former Soviet program, has not furnished evidence of the dismantlement or cessation of key activities, and continues its ongoing secrecy efforts, including [with regard to certain] … military facilities … and legislation criminalizing any disclosure of information about the former Soviet program. The available evidence indicates that Russia has not fulfilled its obligations under Article II to "destroy or divert to peaceful purposes" the BW specified in Article I of the Convention that it inherited from the Soviet Union.[83]

In addition, the US raised its concerns about Russian failures to disclose its contemporary activities, notably that CBMs submitted by the Russian Federation have consistently reported "nothing new to declare" with respect to its biodefence research and development programmes.[84] In its 2019–2022 *Arms Control Compliance Reports*, underlining such Russian reporting discrepancies, the US claimed that "since 2011, the Russian Federation has revised plans and funding to its national chemical and biological facilities that fall under the Russian Ministry of Defense without providing relevant details in their annual CBM reports."[85] The US additionally claimed in its *2022 Arms Control Compliance Report* that:

> Russian government entities remained engaged in dual-use activities during the reporting period, potentially for purposes incompatible with the BWC. The Ministry of Defense related centers 48th Central Scientific Research Institute, Kirov; 48th Central Scientific Research Institute, Sergiev

[81] United States *Arms Control Compliance Report* (2019) op. cit. p. 49.

[82] United States *Arms Control Compliance Report* (2020) op. cit. p. 62; United States *Arms Control Compliance Report* (2021) op. cit. p. 51; United States *Arms Control Compliance Report* (2022) op. cit. p. 40.

[83] United States *Arms Control Compliance Report* (2022) op. cit. p. 40.

[84] United States *Arms Control Compliance Report* (2021) op. cit. p. 51; United States Arms Control Compliance Report (2022) op. cit. p. 39.

[85] United States *Arms Control Compliance Report* (2019) op. cit. p. 49; United States *Arms Control Compliance Report* (2020) op. cit. p. 61; United States *Arms Control Compliance Report* (2021) op. cit. p. 51; United States *Arms Control Compliance Report* (2022) op. cit. p. 39.

> Posad; and 48th Central Scientific Research Institute, Yekaterinburg, which are associated with the Soviet and Russia biological weapons program are undergoing multi-million dollar renovations. Russian Defense Minister Sergey Shoygu has publicly highlighted proposals to modernize the 48th Central Scientific Research Institute by creating a new modern laboratory and research facility.[86]

In its 20 October 2021 response to the authors' information request, the Russian government stated that: "[T]he activities of the Russian Federation in medical and biological sphere is exclusively peaceful and fully complies with the Biological and Toxin Weapons Convention (BWC). This is annually confirmed by the information provided within the BWC confidence building measures." Whilst Russia did not provide any more information to the authors on its CBM declarations, it did state that:

> [T]he Russian Federation is consistently advocating the strengthening of the BWC including by adopting a legally binding protocol thereto on the effective verification mechanism which would enable to confirm States-Parties' compliance with their obligations under the BWC. Pending the 9th BWC Review Conference it would be much required to consolidate efforts by States Parties and international academia in this regard.[87]

6.11 Concluding Remarks

The former Soviet Union conducted an enormous clandestine biological weapons programme during the last century, prior to and following the coming into force of the BTWC, and this reportedly included development of toxin and bioregulator weapons. Moreover, Soviet authorities reportedly argued that development and use of bioregulator weapons was not prohibited by the BTWC. The Soviet biological weapons programme was closed down along with the chemical weapons programme in the early 1990s. The declared chemical weapons stockpile was verifiably destroyed in 2017. However certain States have raised repeated concerns as to whether Russian research and development of biological and toxin weapon subsequently continued. These concerns were deepened due to lack of access to and transparency concerning certain Russian facilities previously

[86] United States *Arms Control Compliance Report* (2022) op. cit. pp. 39–40.

[87] Russian Delegation to the UN Conference on Disarmament, response to an information request from the University of Bradford, 20 October 2021.

involved in Soviet biological weapons development, as well as ambiguous Russian statements concerning new "genetic weapons". In 2020 the US declared that Russia maintains an offensive BW programme and enacted sanctions against certain Russian research institutions.

Open-source information indicates a range of contemporary toxin and bioregulator research, of possible dual-use application, has been carried out including by institutions that were associated in various ways with the former Soviet biological weapons programme. Whilst certain such research has clear medical, protective, or other legitimate applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied.

At least one Russian company reportedly developed a range of delivery mechanisms capable of disseminating RCAs over large areas or extended distances. Potentially a number these could deliver or be adapted to deliver OC and its synthetic analogues. Russia should provide details of which, if any, Russian military, security or police forces acquired these means of delivery, and if so provide details of any existing stockpiles; and the circumstances under which such means of delivery would be employed.

The Soviet Union undertook research and development of a range of ICA/CNS-acting weapons, including those employing pharmaceutical chemicals, toxins, and bioregulators. It is unknown whether subsequent research and development of toxin and bioregulator CNS-acting weapons has been undertaken by Russia and whether stockpiles of such agents remain. In contrast, in 2002 Russia employed an aerosolised CNS-acting pharmaceutical chemical weapon in a large-scale anti-terrorist operation and currently maintains that the law enforcement use of CNS-acting weapons is not regulated by the CWC.

In December 2021 Russia voted against the Decision adopted by CSP 26 prohibiting law enforcement use of aerosolised CNS-acting chemicals and questioned whether this Decision was legitimate. Consequently, it would be beneficial if Russia clarified whether it now accepted this Decision and would implement it fully, including with regard to aerosolised bioregulator or toxin CNS weapons. Similarly, it would be helpful if Russia could clarify whether it considers that bioregulators and other biologically active peptides fall within the definition of toxins or "other biological agents" and whether they are consequently covered under the BTWC, with their development, production, stockpiling, and use as weapons prohibited under that Convention.

Although Russia has submitted CBM reports to the ISU/BTWC States Parties on an annual basis, the completeness and veracity of such reporting has been questioned by at least one State Party. It is unknown whether Russia has submitted Article X reports to the OPCW. Civil society does not have access to these reports as Russia has not published them in the open literature. In combination then these indicators suggest that there remains considerable distrust, in certain quarters, about Russia's dual-use toxin and bioregulator research activities.

It would be beneficial if Russia specifically addressed concerns about its previous and contemporary dual-use toxin and bioregulator research and associated activities through the BTWC CBM annual reporting process and through its annual CWC Article X declaration. To increase public confidence in this area, it would be beneficial if Russia published the unredacted version of all such reports.

Those States that have made public allegations about Russia's previous and contemporary dual-use toxin and bioregulator research and associated activities should employ the relevant consultation and/or investigation and fact-finding mechanisms under the CWC and BTWC, as appropriate, to raise and resolve their concerns.

CHAPTER 7

The Syria Case Study

7.1 Introduction

This case study examines publicly available information concerning Syrian toxin research and associated activities of concern. It highlights the production of ricin by Syria and explores the still unresolved questions regarding the intention behind such activities.

In 1952 Syria acceded to the Geneva Protocol thereby prohibiting the use of chemical, biological and toxin weapons as a method of warfare. It signed the Biological and Toxin Weapons Convention (BTWC) in 1972 but has not, to date, ratified the Convention. As a BTWC signatory State, Syria has rendered political support to the principles of the BTWC and committed itself not to undermine its objectives. Consequently, Syria at a minimum should not "develop, produce, stockpile or otherwise acquire or retain … microbial or other biological agents, or toxins … of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; [or] weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict".[1] However, as a signatory State, Syria has not committed to, nor has it been

[1] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (BTWC), 1972, Article 1. The BTWC text and commentary, and details of States Parties are available at the ICRC Treaties Database, https://ihl-databases.icrc.org/applic/ihl/ihl.nsf/INTRO/450?OpenDocument.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_7

expected to, undertake a range of reporting and transparency measures established by the BTWC States Parties to facilitate confidence in compliance with the Convention—the so-called BTWC confidence-building measures (CBMs). Consequently, Syria has not submitted any annual CBM reports to the BTWC States Parties and Implementation Support Unit (ISU), nor provided any equivalent publicly available information, on research or other activities potentially related to development of toxin (and biological) weapons, to allay concerns that such activities may have been undertaken for malign purposes. As discussed below, Syria did not accede to the Chemical Weapons Convention (CWC) until October 2013. Prior its accession, Syria had not committed itself to be bound by the Convention's prohibitions on the weaponisation of toxic chemicals, including toxins.

7.2 Allegations of Syrian Biological and Toxin Weapons-Related Activities

Certain States, notably the US in their public unclassified reports and statements, repeatedly claimed that Syria had conducted biological weapons research and development. However, it is not always clear from these reports whether Syria's alleged activities included work on toxins, and if so which toxins. Furthermore, publicly available evidence supporting such claims and assessments has been scarce and unverified. In its 2003 *Arms Control Compliance Report*, the US stated that "It is believed that the Syrian offensive BW program is in the research and development stage …. However, the Syrians are not believed to have begun any major effort to put biological agents into weapons."[2] In its 2005 *Arms Control Compliance Report*, the US concluded that "Syria is developing an offensive biological warfare capability that would constitute a violation of the BWC if Syria were a State Party."[3] In its 2010 *Arms Control Compliance Report*, the US asserted that:

> According to available information, Syrian President Bashar Al-Asad stated in 2004 that Syria was entitled to defend itself by acquiring its own chemical and *biological deterrent*. Available information does not indicate that the Syrian Government subsequently modified or rescinded this statement, or

[2] United States (2003) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. Department of State. p. 13.

[3] United States (2005) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. Department of State, August. p. 24.

> that Syria has abandoned all intent to acquire *biological weapons*.[4] (Emphasis added)

In its 2013 *Arms Control Compliance Report*, the US noted that "[I]n 2004, Israel's Intelligence and Terrorism Information Center said in a report on Syria that the Scientific Studies and Research Center had been developing *ricin-based biological weapons*" (emphasis added).[5] In January 2014, James Clapper, Director of National Intelligence, in an unclassified report to the US Senate Select Committee on Intelligence stated:

> some elements of Syria's biological warfare (BW) program might have advanced beyond the research and development stage and might be capable of limited agent production, based on the duration of its longstanding program. To the best of our knowledge, Syria has not successfully weaponized biological agents in an effective delivery system, but it possesses conventional weapon systems that could be modified for biological-agent delivery.[6]

The Syrian government had previously dismissed such allegations or maintained its silence; although on occasion it appeared to indicate the existence of a chemical weapons programme.[7] However, according to certain media reports, on 23 July 2012, Jihad Makdissi, spokesman for the Syrian Foreign Ministry, appeared to imply that the country possessed biological weapons as well as chemical weapons when he stated:

> No chemical or biological weapons will ever be used … during the crisis in Syria no matter what the developments in Syria.... All of these weapons are

[4] United States (2010) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. Department of State, July.

[5] United States (2013) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. Department of State, July. p. 16.

[6] Clapper, J. (2014) *Director of National Intelligence, Statement for the Record, Worldwide Threat Assessment of the US Intelligence Community*, US Senate Select Committee on Intelligence, 29 January. p. 7.

[7] Spiegel International (2009), *SPIEGEL Interview with Syrian President Bashar Assad: Peace without Syria Is Unthinkable*, 19 January. Available at https://www.spiegel.de/international/world/spiegel-interview-with-syrian-president-bashar-assad-peace-without-syria-is-unthinkable-a-602110.html.

> in storage and under security and the direct supervision of the Syrian military and will never be used unless Syria faces external aggression.[8]

Despite this apparent admission of biological weapon and chemical weapon possession, no details were provided of the nature or scale of Syria's biological or chemical weapons stockpiles. This situation, with regard to chemical weapons, dramatically changed following Syria's accession to the Chemical Weapons Convention (CWC) in September 2013.

7.3 Syria's Accession to the CWC and Declaration of a Ricin Chemical Weapons Production Facility

On 14 September 2013, Syria deposited the instrument of accession to the UN Secretary General, requesting to join the Chemical Weapons Convention, and formally acceded to the Convention on 14 October 2013.[9] Following a Decision of the OPCW Executive Council[10] and a parallel UN Security Council Resolution,[11] Syria undertook an expedited chemical weapons disarmament process. Consequently, on 23 October 2013, Syria declared its existing stockpile of chemical weapons and agreed to facilitate their verification and subsequent destruction under the supervision of the OPCW. This initial declaration apparently contained either no information or incomplete information regarding Syria's toxin-related activities. An April 2014 *Reuters* article stated that "[I]n interviews over the last two months with Western officials with access to intelligence about Syria, *Reuters* learned that topics of concern include deadly…agent ricin."[12] According to the US, it together with a number of CWC States Parties raised concerns regarding the "accuracy and completeness of Syria's declaration"; and in April 2014, the OPCW Director General

[8] Associated Press (2012) Syrian regime makes chemical warfare threat. *The Guardian*, 23 July. In contrast, a similar report in the *New York Times* of the Syrian statement was subsequently corrected to remove reference to chemical and biological weapons and replacing it with the term "W.M.D. or unconventional weapons", see: MacFarquhar, N. and Schmitt, E. (2012) Syria Threatens Chemical Attack on Foreign Force. *New York Times*, 23 July.

[9] OPCW (2013) *Press release: OPCW to Review Request from Syria*, 13th September; Executive Council (2013) *Decision: Destruction of Syrian Chemical Weapons*, EC-M-33/DEC.1. OPCW, 27th September; OPCW (2013) *Press release: Syria's Accession to the Chemical Weapons Convention Enters into Force*, 14th October.

[10] Executive Council (2013) op. cit.

[11] Security Council (2013) *Resolution 2118*, S/RES/2118. United Nations, New York, 27 September.

[12] Charbonneau, L. (2014) Western intel suggests Syria can still produce chemical arms. *Reuters*, United Nations, 25 April.

established a Declaration Assessment Team (DAT) "[T]o attempt to resolve many of these concerns, *including toxin-relevant activity*" (emphasis added).[13]

Following the work of the DAT, on 14 July 2014, Syria submitted a further amendment to its initial declaration. Although the full details of Syria's amended declaration have not been made public, a Note by the Director General to the OPCW Executive Council stated that in its amendment "[T]he Syrian Arab Republic declared a CWPF [chemical weapons production facility] … a facility for the production of ricin." The Director General confirmed that "[T]he newly declared facility is subject to verification and destruction." The Director General also stated that "[A]ccording to the amendment, the entire quantity of ricin produced was disposed of prior to the entry into force of the Convention for the Syrian Arab Republic."[14]

If Syria had still possessed these ricin stockpiles following its accession to the CWC, it would have been required, under the CWC, to declare all quantities of such stockpiles, the location of chemical weapons storage facilities, nature of the storage, that is, whether the ricin was held in "munitions, sub-munitions, devices, equipment or bulk containers and other containers".[15] Furthermore, Syria would have been required to facilitate OPCW verification of its stockpile declaration through on-site visits and then verification of all stockpile destruction.[16] Because Syria destroyed its ricin stockpiles at some stage before accession, it was not obliged to provide the OPCW with full details of this stockpile nor for it to undergo associated OPCW verification concerning this stockpile.[17] Furthermore,

[13] United States (2015) *Report on Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments, Biological and Toxin Weapon Convention, Syria*, 5 June. p. 20. Available at https://2009-2017.state.gov/t/avc/rls/rpt/2015/243224.htm#BWC.

[14] Executive Council (2014) *Note by the Director-General, Progress in the elimination of the Syrian chemical weapons programme*, EC-M-44/DG.1, Section 4. (b), OPCW, The Hague, 25 July.

[15] Chemical Weapons Convention (1993) Part IV(A)—*Destruction of Chemical Weapons and Its Verification Pursuant to Article IV*, A, I (a)–(c).

[16] Chemical Weapons Convention (1993) Part IV(A)—*Destruction of Chemical Weapons and Its Verification Pursuant to Article IV,* C.

[17] It should be noted that certain other CWC States Parties had previously destroyed their chemical weapons stockpiles before entry into force of the CWC in 1997. Such actions have clearly left open questions with regard to the nature, size, location, and so on, of their former CW stockpiles.

because of standard OPCW confidentiality practices (contained in a Confidentiality Annex to the CWC),[18] the Organisation has provided no public details of the information Syria submitted to the OPCW concerning its ricin stockpile.

However, on 29 May 2022, in correspondence to the current authors, the Permanent Mission of Syria to the OPCW stated that: "All of the detailed information relating to the Ricin production programme has been fully shared with the Technical Secretariat of the OPCW, and in accordance with the CWC, through declaring the mentioned programme and its strategy, as well as fully disclosing the Ricin production amounts and dates, as well as the dates of their destruction."[19]

Notwithstanding the Syrian Permanent OPCW Missions' correspondence to the authors, very little information is publicly available concerning the nature and scale of Syria's ricin production prior to accession, nor regarding the intended use (or uses) to which its ricin stockpiles would be put, that is, whether they were for medical or other peaceful purposes, or were instead part of a toxin weapons programme. Zanders, who is one of the few observers to publicly examine this issue,[20] has noted that:

> Syria apparently cultivated castor oil plants (*Ricinus communis*)—[from which ricin is extracted]—on several tracts the size of football fields. In itself, this is not so unusual as the oil makes for an excellent lubricant for heavy engines, such as those in military lorries. However, Syria's initial explanation [to the OPCW of the purpose for its ricin production] referred to cancer research and treatment, which was wholly implausible in view of the minute quantities of ricin required for [such medical] research.[21]

[18] Chemical Weapons Convention (1993) Annex on the Protection of Confidential Information "Confidentiality Annex."

[19] Syria (2022) Permanent Mission of Syria to the OPCW, response to an information request from the University of Bradford, received by email on 29 May 2022. The Permanent Mission also stated that: "The Syrian Arab Republic has fulfilled all of its obligations due to its accession to the CWC … [It] has effectively and fully destroyed its entire chemical weapons stockpile in coordination with the Technical Secretariat of the OPCW, and in accordance with the Chemical Weapons Convention (CWC), and has done so in record time that is unprecedented by any other member state, despite the very challenging and difficult circumstances which Syria has undergone."

[20] See also Jeremias, G. et al. (2016) *Spotlight on Syria's biological weapons*, 8 February. Available at https://www.armscontrolwonk.com/archive/1201010/guest-post-spotlight-on-syrias-biological-weapons/#comments; Meier. O (2016) Governance or Arms Control? The Future of the Biological and Toxin Weapons Convention, 26 October. Available at https://www.cfr.org/councilofcouncils/global-memos

[21] Zanders, J. P. (2014) Gradually making sense of Syria's CW declarations, *The Trench*, 11 August. Available at https://www.the-trench.org/syrias-cw-declarations.

A September 2014 *Reuters* article highlighted continuing scepticism amongst certain States regarding Syria's purported reasons for not initially reporting the ricin production facility (and two other unconnected chemical production facilities) in its initial declaration to the OPCW. According to one unnamed 'diplomatic source', "[I]nformation is having to be extracted, piece by piece, demonstrating that he (Syrian President Assad) didn't properly come clean when he joined the convention." Furthermore, an unnamed "diplomatic source" stated that: "[S]yria will argue that the facilities were not revealed earlier because they were in a rush when they first had to report them …. They had said the ricin was for medical purposes, but we don't believe that's true."[22]

On 19 November 2014, a "[C]ombined plan for the destruction and verification of the "'Al-Maliha' ricin production facility" was adopted by the OPCW Executive Council.[23] Although there has been very limited publicly available information disclosed by the OPCW, there were considerable delays in completing destruction caused by the unstable security situation as the ricin production facility was located in an area not under Syrian government control. According to Major General Igor Kirillov, Chief of Russian Armed Forces' Radiological, Chemical and Biological Defense Troops, the "facility, in Al Maliha, was destroyed by the Syrians on June 8, 2018 … and the proof was sent to the OPCW.."[24] On 24 July 2018, the OPCW reported that the Technical Secretariat had verified the destruction of all of Syria's declared "chemical weapons production facilities", with the destruction of the final two facilities taking place took place on 7 June and 23 June, respectively. On 12 July, the OPCW Technical Secretariat "conducted inspections at both sites and verified that all declared buildings had been razed to ground level and all debris removed."[25]

[22] Deutsch, A. (2014) Exclusive: Syria reveals more chemical weapons facilities to watchdog—sources. *Reuters*, 17 September.

[23] OPCW (2014) *Decision: Combined Plan for Destruction and Verification of the "Al-Maliha" Ricin Production Facility in the Syrian Arab Republic*, EC M 46/DEC.1, 19 November.

[24] Russia (2018) Equipment in Syria's Douma Chemical Lab Made in EU, N America. Russian Ministry of Defence, 22 June. Available at https://sputniknews.com/middleeast/201806221065657552-chemical-weapons-russia-syria-europe/.

[25] OPCW (2018) *Note by the Director General, Progress in the elimination of the Syrian chemical weapons programme*. Executive Council, EC-89/DG.1, 24 July.

Whilst the Al-Maliha ricin production facility has now been verifiably destroyed, a number of important questions and uncertainties still need to be addressed concerning the nature of the activities previously undertaken there. No public information is available concerning the size and nature of the facility, the amount of ricin produced annually, when ricin production commenced and halted, what became of the ricin produced over this period, when ricin stockpiles were destroyed and by whom. Furthermore, absolute clarity is needed regarding the purpose or purposes behind Syrian ricin production. To date, the Syrian government has not publicly admitted that the ricin produced at Al-Maliha was intended for use in toxin weapons; instead as noted earlier, it reportedly claimed that the ricin was destined for medical purposes, i.e. use in cancer research and treatment. This assertion appears to conflict with Syria's formal declaration of the facility to the OPCW as a *chemical weapons production facility (CWPF)*—and Syria's verifiable destruction of this CWPF as required under the Convention—as such a CWPF designation specifically excludes a "single small-scale facility for production of chemicals listed in Schedule 1 *for purposes not prohibited under this Convention* (Emphasis added)."[26] Clearly there is an open question here that needs to be resolved: if the Al-Maliha ricin production facility was solely intended for medical or other civilian purposes why didn't Syria simply present evidence to the OPCW proving this was the case, rather than declaring it to be a chemical weapons production facility that subsequently had to be destroyed under the CWC?

Zanders has highlighted the difficulties of weaponising ricin[27] and noted that "whilst none of these problems are insurmountable, the net effect is that the agent is more cumbersome to weaponise or less effective on the battlefield than alternatives."[28] He also noted the scepticism of "several Western officials" he contacted over "public Israeli reports on Syria's ricin [weapons] programme", and further that the US stopped referring to Syria's ricin-based biological weapons programme in its *Arms*

[26] Chemical Weapons Convention, Article II, 8 (b) (iii).

[27] Zanders, J. P. (2014) op. cit.

[28] Conversely, despite the difficulties of its weaponization, notably aerosolisation, and the consequent limitations of ricin as an effective wide area battlefield weapon intended to cause large scale incapacitation or fatality, it may still be perceived as having utility in armed conflict as a toxin weapon primarily intended to spread fear amongst combatants and civilians. Alternatively, it may have perceived utility as a targeted toxin assassination weapon. The reported Soviet Union development of ricin-based assassination weapons is described in Chap. 6 of this publication.

Control Compliance Reports from 2014 onwards. He has posited that Syria's actions "might reflect a compromise with the OPCW to remove any ambiguity about the purpose of the ricin resulting from a particular [castor oil] production process in view of the need for absolute certainty that all aspects of the country's CW programme have been eliminated." However, he noted that, "Right now the reason behind Syria's declaration of a CW production facility exclusively dedicated to ricin manufacture remains murky."[29]

It appears that certain States, at least publicly, subsequently maintained that the ricin produced at Al-Maliha was intended for weaponisation and that Syria had acknowledged this. For example, in his September 2020 statement to the UN Security Council briefing on Syrian chemical weapons, UK Ambassador Jonathan Allen declared that "Since their initial declaration in 2013, *the Syrian authorities have themselves admitted to having produced chemical weapons not in the original declaration. That includes Ricin, which the Syrian authorities admitted in 2014*" (emphasis added).[30] Given the previous, and repeated, obfuscation of its chemical weapons programme, there is legitimate concern as to whether Syria has been completely forthright over its activities at Al-Maliha, and whether any further production facilities or stockpiles of ricin or other potential toxin weapons remain.

7.4 Concluding Remarks

Certain States alleged that Syria had both a biological weapons and a chemical weapons development programme, and a 2012 Syrian government statement seemed to imply possession of such weapons. Syria acceded to the CWC in 2013, but concerns were raised about the accuracy and completeness of its initial declaration—including with regard to production and stockpiles of ricin. An amended declaration stated that all ricin stocks had been destroyed prior to entry into force of the Convention. A ricin chemical weapons production facility (CWPF) was declared, and verifiably destroyed in 2018. Much public uncertainty remains about this

[29] Zanders, J. P. (2014) op. cit.

[30] United Kingdom (2020) *Statement by UK Ambassador Jonathan Allen at a UN Security Council briefing on Syrian chemical weapons.* United Nations, 10 September. Available at https://www.gov.uk/government/speeches/addressing-the-use-of-chemical-weapons-in-syria.

former ricin CWPF, including the quantities, intended and actual employment of the ricin produced.

While Syria has provided the authors with some relevant information, due to the OPCW's confidentiality measures, there is no public confirmation that Syria has submitted full details of its former production, stockpiles and employment of ricin, to the OPCW. If it has not yet done so, it should provide all such information to the OPCW, including full details of the intended and actual purposes of ricin production, the annual quantities of ricin produced, the final quantity of ricin stockpiled prior to destruction, the location of the ricin storage facilities, the nature and disposition of its storage, as well as evidence of its complete destruction. Syria should also provide full details of any further toxin weapon development, production or storage. Although it is not obliged to do so under the CWC, to increase public confidence in this area, it would be beneficial if Syria published the unredacted version of all the information detailed above.

In addition, if it has not already done so, Syria should provide the OPCW with full details of any research and associated activities related to the weaponisation of bioregulators or toxins it has undertaken for "protective purposes". Although such activities are permitted under the CWC, all States Parties are required to report them to the OPCW Technical Secretariat under annual Article X declarations. Once again, although not obliged to do so, it would be beneficial if Syria published the unredacted version of all such information.

If CWC States Parties have continuing concerns regarding Syria's previous ricin production at Al-Maliha, or with regard to whether any further production facilities or stockpiles of ricin or other potential toxin weapons remain, they should employ the appropriate consultation, investigation, and fact-finding mechanisms under the CWC to raise and resolve their concerns.

Whilst Syria is not a BTWC State Party, it is a signatory State and as such has committed itself not to undermine the Convention's objectives including with regard to the prohibition on development, production and stockpiling of toxin weapons. Consequently, Syria's declaration and subsequent delayed destruction of a CWPF for manufacturing ricin, and the unanswered questions still remaining regarding the intention behind Syria's ricin production, are areas of valid concern for BTWC States Parties. However, as far as we are aware, no BTWC State Party formally raised this issue during relevant public BTWC meetings at the time or subsequently, as a matter to be collectively addressed through the

BTWC. It is not known whether the BTWC States Parties and the ISU were formally informed by the OPCW of Syria's declaration regarding its CWPF for ricin production and its former ricin stockpiles. Given the overlap between the BTWC and CWC with regard to toxins, it would have been appropriate and beneficial if such information exchange had occurred, and processes to ensure formal information exchange in any similar future circumstances should be established. To build further confidence regarding Syria's intentions to respect the norm prohibiting toxin and biological weapons, Syria should initiate the process of accession to the BTWC and commit to engage fully in all its mechanisms, including its confidence-building measures.

CHAPTER 8

The US Case Study

8.1 US Offensive Biological Weapons Programme and Its Termination

An initial US biological weapons programme began after World War I and included limited research and development of the toxin ricin. The US Chemical Warfare Service (CWS) explored adhering ricin to bullets and also disseminating it as a dust cloud.[1] However, findings from these activities were never utilised. From 1945 till 1969, the US pursued a far more expansive biological weapons programme comprising research, development, and production of a range of biological and toxin weapons intended for offensive purposes. This included biological weapons that utilised toxins notably botulinum toxin, staphylococcal enterotoxin B (SEB), and saxitoxin. There is no confirmed evidence that any of these weapons were employed in either armed conflict or for other offensive purposes.[2]

The original version of this chapter was revised with text deleted. The correction to this chapter can be found at https://doi.org/10.1007/978-3-031-10164-9_11

[1] Smart, J.K. (1997) History of Chemical and Biological Warfare: An American Perspective, Chapter 2, in: F. R. Sidell. E. T. et al. (Eds), *Medical Aspects of Chemical and Biological Warfare*. Office of the Surgeon General, Department of the Army, Washington DC, 1997. (pp. 21–22).

[2] National Threat Initiative (NTI), *United States Biological Overview*. Available at https://www.nti.org/analysis/articles/united-states-biological.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_8

In 1969, US President Nixon issued a *Statement on Chemical and Biological Defense Policies and Programs* in which he declared that: "[T]he United States shall renounce the use of lethal biological agents and weapons, and all other methods of biological warfare. The United States will confine its biological research to defensive measures such as immunization and safety measures".[3] Immediately following this statement, a bureaucratic debate ensued over how the US should address toxins, owing in part to the question of whether toxins should be considered as being chemical or biological weapons.[4] The Department of Defense (DoD) viewed toxins as chemical weapons that should not be banned. In addition, the military believed that toxins offered advantages over other chemical weapons because of their high potency per unit weight and their multiple effects.[5] By contrast, the Department of State viewed toxins as biological weapons since the toxins in question, botulinum toxin and staphylococcal enterotoxin B (SEB), were both derived from bacteria using equipment similar to that used for creating *Bacillus anthracis* spores.[6]

On 14 February 1970, following a formal policy review process, President Nixon issued a *Decision* under which the US renounced "offensive preparations for and the use of toxins as a method of warfare"; and confined "its military programs for toxins, whether produced by bacteriological or any other biological method or by chemical synthesis, to research for defensive purposes only, such as to improve techniques of immunization and medical therapy." The president further "directed the destruction of all existing toxin weapons and of all existing stocks of toxins which are not required for a research program for defensive purposes only". The *Decision* also stated that the US would "have no need to operate any facilities capable of producing toxins either bacteriologically or biologically in

[3] United States (1969) *Statement on Chemical and Biological Defense Policies and Programs*, 25 November. Public Papers of the Presidents. Department of State, Washington, D.C. p. 968.

[4] NTI *United States Biological*. op. cit.

[5] Tucker, J. and Mahan, E. (2009) *President Nixon's Decision to Renounce the U.S. Offensive Biological Weapons Program*. Case Study 1, Center for the Study of Weapons of Mass Destruction, National Defense University, October. p. 11.

[6] Tucker, J. and Mahan, E. (2009) op. cit. pp. 12–14.

large quantities and therefore also capable of producing biological agents."[7]

A *National Security Decision Memorandum* on toxins, NSDM–44, facilitating implementation of Nixon's renunciation, was subsequently issued on 20 February 1970.[8] Tucker and Mahan argue that by extending the unilateral ban on biological weapons to cover all toxins, regardless of their means of production, Nixon's decision closed the potential loophole that would have been created by the future chemical synthesis of toxin agents and resulted in a US policy that was "cleaner and less ambiguous".[9]

The US biological and toxin weapons stockpile was catalogued in 1970. According to a September 1970 Department of Defense memorandum, the stockpile contained: 13 pounds of botulinum toxin and 71 pounds of SEB. In addition, there was 10.9 pounds of toxin (botulinum and/or saxitoxin) in filled munitions.[10] All biological and toxin munitions and offensive weapons stockpiles were subsequently destroyed.

The US unilateral biological and toxin weapon ban greatly helped to facilitate the rapid negotiation of the 1972 Biological and Toxin Weapons Convention (BTWC) with its international prohibitions on development, production, stockpiling, and transfer of these agents. In 1974, President Ford submitted the BTWC and the 1925 Geneva Protocol simultaneously to the US Senate for its advice and consent to ratification. Consent was duly granted on 16 December 1974, and the BTWC entered into force on 26 March 1975.[11] The US subsequently signed the Chemical Weapons Convention (CWC) in 1993 and ratified the Convention in 1997.

[7] Office of the White House Press Secretary (Key Biscayne, FL) (1970) *Statement on Toxins*, February 14 in, Document 189. Available at www.state.gov/r/pa/ho/frus/nixon/e2/83628.htm.

[8] *National Security Decision Memorandum 44*, Washington, DC, February 20, 1970. In *Foreign Relations of the United States*, Document 190. Available at www.state.gov/r/pa/ho/frus/nixon/e2/83628.htm.

[9] Tucker, J. and Mahan, E. (2009) op. cit. p.16.

[10] Department of Defense (1970) *Environmental Impact Statement for Disposal of Biological Agents and Weapons*. Washington, D.C. 17 September. As cited by Van Courtland Moom, J. (2006) The US Biological Weapons Program. Chapter 2 in M. Wheelis et al. (Eds.) *Deadly Cultures: Biological Weapons Since 1945*. Harvard University Press, Harvard.

[11] Tucker, J. and Mahan, E. (2009) op. cit.

8.2 The US Search for Incapacitating Chemical Agent (ICA)/Central Nervous System (CNS)-Acting Weapons[12]

8.2.1 Activities Prior to the 1970 Presidential Decision

There is a considerable amount of information in the public record about the search for 'incapacitating chemical agent' (ICA) weapons by the US since World War II. Whilst this research and development concentrated upon certain classes of pharmaceutical chemicals,[13] the US also explored the potential utility of employing toxins and bioregulators for such purposes. During the 1960s, staphylococcal enterotoxin B (SEB) was extensively investigated as an ICA weapon in the US CBW programme.[14] SEB has an inhalation ED_{50} in humans estimated to be at least three orders of magnitude smaller than the corresponding LD_{50} of nerve-agents such as sarin or VX.[15] Whilst high-dose, microgram-level exposures to SEB will

[12] Whilst this section concentrates on toxin and bioregulator research and associated activities potentially related to ICA/CNS-acting weapons, the US undertook parallel activities exploring a range of pharmaceutical chemicals as potential ICA/CNS-acting weapons. In the 1960s, the US developed ICA weapons containing BZ (3-quinuclidinyl benzilate). There are no confirmed reports of their use in armed conflict, and all stockpiles were destroyed in the late-1980s and 1990s. The US subsequently conducted research into pharmaceutical chemical-based ICA weapons for both military and law enforcement purposes, prior to and after the coming into the CWC, although there is no evidence of completed development or production of such weapons. For further discussion see: Crowley, M. (2016) *Chemical Control: Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery*. Palgrave, Basingstoke, pp. 31–35; Crowley, M. and Dando, M. R. (2014) *Down the Slippery Slope? A Study of Contemporary Dual-Use Chemical and Life Science Research Potentiallty Applicable to Incapacitating Chemical Agent Weapons*. University of Bradford and University of Bath, pp. 60–73; Davison, N. (2009*) Non-Lethal Weapons*. Palgrave Macmillan, Basingstoke.

[13] For further discussion see: Crowley, M. (2016) *Chemical Control: Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery*. Palgrave, Basingstoke; Crowley, M. and Dando, M. R. (2014) *Down the Slippery Slope? A Study of Contemporary Dual-Use Chemical and Life Science Research Potentiallty Applicable to Incapacitating Chemical Agent Weapons*. University of Bradford and University of Bath; Davison, N. (2009) *Non-Lethal Weapons*. Palgrave Macmillan, Basingstoke.

[14] US Army Test and Evaluation Command (1982) *Joint CB Technical Data source Book, Volume VI, Toxin Agents, Part Two: Agent PG*. DTC 73 - 33, US Army Deseret Test Center, Fort Douglas, Utah. June.

[15] Perry Robinson, J. (2008) Bringing the CBW Conventions Closer Together, *CBW Conventions Bulletin*, **80**, 1–4, p. 3.

result in fatalities, inhalation exposure to nanogram or lower levels may be severely incapacitating.[16] In 1968, during DTC Test 68-50, dry-agent spray tanks filled with SEB (referred to by the US as Agent PG) mounted on US *Phantom* strike aircraft allowed the agent to be released 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 km^2.[17] In addition to such large-scale testing, US documents indicate that by the beginning of 1970, the US had the production capacity to make 600 pounds of SEB per month[18]—although there are no confirmed publicly available records of the total agent quantities produced. As far as is known, SEB was never employed as a weapon, and all US research, development, and production of such offensive toxin weapons ended with the moratorium announced by President Nixon on 14 February 1970, and SEB stocks for offensive weapons were subsequently destroyed.[19]

8.2.2 Military Dual-Use Research Programmes After the 1970 Decision

The US incapacitating chemical weapons programme continued during the 1970s and 1980s. Whilst there is evidence that this programme explored a wide range of pharmaceutical chemicals, it is unknown whether research extended to toxins and bioregulators during this period.[20] In the 1990s, the US conducted dual-use research, including on bioregulators and bioregulatory systems, applicable to the study and potential

[16] Ulrich, R. et al. (2007) Staphyloccocal Enterotoxin B and Related Toxins, Chapter 14 in: M. Lenhart, D. Lounsbury and J. Martin (Eds.) *Medical Aspects of Biological Warfare*. Office of the Surgeon General. pp. 311–322. p. 312.

[17] Perry Robinson, J. (2008) op. cit.

[18] Interdepartmental Political-Military Group in response to NSSM 85 (1970) *Report to the National Security Council: US Policy on Toxins*, January 1970. Declassified by the US Department of State, August 2007 in Document 177 in Department of State, Office of the Historian (2007) *Foreign Relations of the United States: Nixon-Ford Administrations*, volume E-2: Documents on Arms Control and Nonproliferation, 1969–1972. p. 5.

[19] Office of the White House Press Secretary, Key Biscayne, FL (1970) op. cit.; Tucker, J. and Mahan, E. (2009) op. cit. pp. 13–17; Van Courtland Moon, J. (2006) op.cit. pp. 36–39.

[20] For further discussion see: Crowley, M. (2016) op. cit.; Crowley, M. and Dando, M. R. (2014) op. cit.; Davison, N. (2009) op. cit.

development of incapacitating chemical agent weapons.[21] Certain activities were carried out for purportedly defensive purposes, under the auspices of the Chemical and Biological Defense Command (CBDCOM) and its largest component, the Edgewood Research Development and Engineering Center (RDEC), whose mission was stated as being to "conduct and manage basic and applied research, development, engineering and sustainment for chemical and biological defence systems and equipment."[22] An analysis by Dando of RDEC research paper abstracts published and reported at its annual conferences indicated interest in the μ-opioid receptors, analgesic opioids and their synthetic analogues, notably fentanyl;[23] and a second line of research into the locus coeruleus (LC) system of the mammalian brain that is required for alert activity, associated alpha$_2$ adrenergic receptors, sedative adrenergic agonists notably noradrenaline, and their synthetic analogues notably medetomidine.[24]

Other applicable research was undertaken by the US Army Medical Research Institute of Chemical Defence (MRICD) whose scientists: "*conduct research to characterise the effects of* various chemical warfare agents and *selected biological neurotoxins. They seek to define what biological systems are affected by the* agent or *toxin, and what short- and mid-term consequences of exposure are*" (emphases added).[25] This theme of attempting to discover the precise biological systems (receptors and circuits) became of increasing importance for the US military as the biotechnology revolution progressed during this century.

Further related research, including into the LC and its neurons, was undertaken by the US Air Force Office of Scientific Research (AFOSR) notably under its Neuroscience Programme. This Programme had the stated intention of understanding the neural mechanism which supports effectiveness in carrying out skilled tasks in demanding circumstances. "[A]reas of emphasis" for the Programme were "fundamental studies of the neurobiological mechanisms underlying neurological responsiveness,

[21] Dando, M. R. (1996) *A New Form of Warfare: The Rise of Non-Lethal Weapons*. Brassey's, London. See Chapter 8: An Assault on the Brain. pp. 157–168.

[22] Hartford County Chamber of Commerce (1995) *Military Appreciation Week: Aberdeen Proving Ground*, 14–20 May; as cited in Dando, M. R. (1996) op. cit. p. 158.

[23] Dando, M. R. (1996) op. cit. pp. 158–160.

[24] Dando, M. R. (1996) op. cit. pp. 161–168.

[25] Hartford County Chamber of Commerce (1995) Military Appreciation Week: Aberdeen Proving Ground, 14–20 May; as cited in Dando, M. R. (1996) op. cit. p. 158.

learning and memory, fatigue, stress, attention and arousal."[26] Analysis by Dando of AFOSR-funded research highlighted a range of papers exploring the LC and the anatomy, physiology, and pharmacology of its neurons, with numerous studies employing rat and monkey models. In addition, other AFOSR research focused on the "role of brain serotonin".[27] This is of relevance as Serotonin (5-hydroxytryptamine) is a major neurotransmitter produced by neurons in the lower parts of the brain but having axons that distribute widely throughout the CNS and having involvement in diverse functional circuits such as anxiety and learning and memory.[28]

8.2.3 The Pennsylvania State University Study

These themes and lines of research were again taken up in the highly influential joint report on "calmatives" by researchers at the Applied Research Laboratory and the College of Medicine at Pennsylvania State University published in October 2000. The study investigated a wide range of potential calmative agents for counterterrorism and other law enforcement purposes. Although concentrating on pharmaceutical chemicals, it also identified two bioregulatory peptides and associated bioregulatory systems of interest.[29] The first bioregulator discussed was corticotropin-releasing factor (CRF), a peptide that triggers the release of stress-related hormones. Concentrated in the hypothalamus of the brain, CRF binds to two classes of receptors that are closely linked to feelings of anxiety and stress. In principle, receptor antagonist peptides or synthetic analogues that block CRF receptors in the brain could induce a "calm behavioral state".[30] The second bioregulatory peptide examined was cholecystokinin (CCK) which is present in the body in several biologically active forms. There are two classes of CCK receptors, CCK-A receptors concentrated in

[26] Air Force Office of Scientific Research, Research Interests and Broad Agency Announcements 95-1, Bolling Air Force Base, Washington, DC, as cited in Dando, M. R. (1996) op. cit. p. 166.

[27] Dando, M. R. (1996) op. cit. p. 167.

[28] See Meyer, J. S. and Quenzer, L. F. (2013) *Psychopharmacology: Drugs, the Brain and Behaviour*, (Second Edition). Sinauer Associates, Sunderland, Mass. Chapter 6 Serotonin. pp. 167–184.

[29] Lakoski, J. M. et al. (2000) *The Advantages and Limitations of Calmatives for Use as a Non-Lethal Technique*. Applied Research Laboratory, College of Medicine, Pennsylvania State University; for further discussion see: Tucker, J. (2008) The body's own bioweapons. *Bulletin of Atomic Scientists*, **64**(1), 16–22; Crowley, M. (2016) op. cit.

[30] Lakoski, J. (2000) op. cit. pp. 39–42.

the gastrointestinal tract, and CCK-B receptors in the central nervous system. Synthetic CCK analogues that stimulate CCK-B receptors trigger panic attacks, disruption of memory, and increased sensitivity to pain; synthetic CCK antagonists that block these receptors induce a tranquil state and could therefore serve as potential calmative agents.[31]

8.2.4 US Air Force Bioscience Research Programme

On 1 October 2009, the Air Force Office of Scientific Research (AFOSR) issued an initial solicitation for a $49 million multi-project research programme entitled *Advances in Bioscience for Airmen Performance* (BAA-09-02-RH).[32] Under this announcement, the 711th Human Performance Wing, Human Effectiveness Directorate solicited "white papers…for innovative science and technology projects to support advanced bioscience research." Specifically, the Biosciences and Performance Division was seeking "unique and innovative research concepts" that address its four "technical mission areas" which included "biobehavioral performance."[33]

Although the over-arching goal of the "biobehavioral performance" mission area was to "develop bio-based methods and techniques to sustain and optimize airmen's cognitive performance", it included *inter alia*:

> (a) Development of effective, reliable, and affordable alertness management, performance enhancing and emotional state modulation technologies. Includes nonmedical neuroscience and biochemical pathway techniques.

[31] Lakoski, J. (2000) op. cit. pp. 42–45.

[32] Air Force Office of Scientific Research (AFOSR) (2009) *Advances in Bioscience for Airmen Performance BAA-09-02-RH*. Department of Defense, 1st October. This together with subsequent revisions, available from https://www.fbo.gov/?s=opportunity&mode=form&tab=core&id=0b237485b3d66e02ad7e4b94588069e0&_cview=0.

[33] The three other "technical mission areas" were: Applied Biotechnology—Goal is to develop and exploit advances in biotechnology and associated nanotechnologies to enhance performance and situational awareness of the force; Vulnerability Analysis—Goal is to rapidly identify human threat conditions and sustain/expand Airmen performance in stressful environments. It includes research in physical and physiological biosignatures, neuroscience, anthropometry, biomechanics, human modelling, database networking, and data mining; Counterproliferation—Goal is to improve the Air Force's ability to locate, identify, track, target, and destroy biological warfare agents (BWA) and other weapons of mass destruction (WMD), as well as anticipate and mitigate WMD effects on AF operations. Air Force Office of Scientific Research (1 October 2009), op. cit.

> (b) Conversely, *the chemical pathway area could include methods to degrade enemy performance and artificially overwhelm enemy cognitive capabilities.* (Emphasis added)[34]

On 11 September 2014, following a request by the current authors for further information on this programme, a US Department of Defense (DoD) official stated that: "[T]he purpose of the program text for the bio behavioral performance technical area, including the [highlighted] statement…was to be inclusive of all potential chemical pathways areas for study in order to sustain and optimize cognitive performance."[35] The DoD official further stated that:

> Research related to the study of chemical pathways was contained in the biobehavioral performance technical area of the research program. However, no grant was awarded for work under this technical area. Grants were awarded for work in other technical areas, but that work does not involve ICA [incapacitating chemical agent] research. The solicitation of and granting of any work under this project is compliant with the Chemical Weapons Convention.[36]

8.2.5 The DARPA Oxytocin Project

Oxytocin is an evolutionarily conserved neuropeptide—a bioregulatory chemical found in the brain—which has been extensively studied for several decades and is known to be involved in the regulation of complex behaviours such as reproduction, lactation, attachment, pair bonding and social recognition in mammals.[37]

In June 2005 *Nature* carried a paper entitled "Oxytocin increases trust in humans."[38] The paper reported a study of human behaviour in a game designed to test levels of trust. The game was played in two different conditions: in one, people were not given a dose of oxytocin by intra-nasal

[34] Air Force Office of Scientific Research (2009), op. cit.

[35] Correspondence to Dr M.Crowley, BNLWRP, from Ms. Cynthia O. Smith, Department of Defense Spokeswoman, the Defense Press Office, Office of the Assistant Secretary of Defense (Public Affairs), United States of America, 11th September 2014.

[36] Correspondence to BNLWRP from the U.S. Defense Press Office, (2014) op. cit.

[37] See for example, Quintana, D. S. et al. (2019) Oxytocin pathway gene networks in the human brain. *Nature Communications*, 10, 688. https://doi.org/10.1038/s41467-019-08503-8.

[38] Kosfeld, M. et al. (2005) Oxytocin increases trust in humans. *Nature*, **435**, 673–676. p. 675.

administration before they played, and in the other, the oxytocin was given. According to the paper, the researchers found "that intranasal administration of oxytocin causes a substantial increase in trusting behaviour". This study initiated a resurgence of interest in oxytocin as a neuromodulator in the brain.

In 2013, the US Defense Advanced Research Projects Agency (DARPA) put out a solicitation for work entitled "Oxytocin: Improving measurements sensitivity and specificity". The solicitation addressed oxytocin's role as a neurotransmitter and explained that "Oxytocin…affects behaviours relevant to national security."[39]

The DARPA solicitation explained that:

> Recent studies have shown the regulation of oxytocin to be a complex process. In particular two forms of oxytocin have been identified. A 10–12 amino acid pro-hormone is first produced, and then, at some point, may be cleaved to a 9 amino acid hormone. This shortened form is the active neuropeptide, oxytocin, known to bind the oxytocin receptor and is credited with oxytocin's behaviour altering effects.[40]

As then available techniques were not able to distinguish between the different forms of oxytocin, DARPA was interested in funding the development of new techniques that could. The specific rationale highlighted for this solicitation was to help to better understand how "Narrative Networks" influence people's behaviour—in short, how we are influenced by stories told by people we trust. As the solicitation explained:

> The DARPA program Narrative Networks is examining oxytocin in this context and would benefit from increased measurement specificity and sensitivity. Developments made under this SBIR effort could be transitioned, in synergy with findings from Narrative Networks, to provide better assays of oxytocin as it changes with narrative influence.

The "narrative networks" research project was not intended towards the development of ICA/CNS-acting weapons in the narrow sense. However, the investigation of oxytocin and its role in the formation of trust, and

[39] Defense Advanced Research Projects Agency (2013) *Oxytocin: Improving Measurement Sensitivity and Specificity*. SBIR Solicitation, 2013.2, Department of Defense. p. 1.

[40] (2013) Defense Advanced Research Projects Agency, op. cit. p. 1.

how this biological process can be manipulated, does have potential dual-use applicability to the development of ICA/CNS-acting weapons.

8.2.6 US Brain Initiative

Over the past two decades, the technologies available to neuroscientists have developed rapidly and made it increasingly possible to understand the neuronal circuits in the CNS that underlie our behaviours. The obvious advantages of this work, for example, in helping people with brain dysfunctions and injuries, have led States, including the US, to initiate large-scale brain research projects over recent years.

The US Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative was launched in 2013, as a public private partnership with about $100 million in the President's Fiscal Year 2014 Budget.[41] It is notable that approximately half of the US funding came from the DoD and DARPA.[42]

The potential for investigating the neural circuits producing human behaviour was highlighted in the scoping report for the US BRAIN project which stated:[43]

> In considering these goals and the current state of neuroscience, the working group identified the analysis of circuits of interacting neurons as being particularly rich in opportunity with potential for revolutionary advances.

The report further stated that:

> Truly understanding a circuit requires identifying and characterizing the component cells, defining their specific connections with one another, observing their dynamic patterns of activity as the circuit functions *in vivo* during behaviour, *and perturbing these patterns to test their significance*. It also requires an understanding of the algorithms that govern information

[41] The White House (2013) *Fact Sheet: BRAIN Initiative*, 2 April. Available at www.whitehouse.gov/the-press-office/2013/04/02/fact-sheet-brain-initiative.

[42] Ibid. p. 2.

[43] Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Working Group (2014) Report to the Advisory Committee to the Director, NIH: *Brain 2025: A Scientific Vision*. National Institutes of Health, 5 June, p. 5; as cited in Dando, M. R. (2018) Advances in Understanding Targets in the Central Nervous System. Chapter 8 in M. Crowley, M. et al. (Eds.) (2018) *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*. Royal Society of Chemistry, London. p. 230.

> processing within a circuit and between interacting circuits in the brain as a whole. (Emphasis added)

In Chap. 2 we noted that the advances in the life sciences could be viewed as a game changer for those intent upon development of biological and chemical weapons as more and more was revealed about the human CNS, as well as other regulatory immune and physiological systems that could be attacked or malignly manipulated with ever greater precision through specifically designed and delivered agents. Of course, many of the very same life science advances and human physiological systems are the focus of the US and other States' brain research but for benign purposes: to find means of helping people when these circuits go wrong. The website of the US BRAIN Initiative details how these legitimate aims are to be achieved and lists grants awarded and publications produced. A 2020 analysis by Dando of the BRAIN initiative's grants and publications has explored the range of behavioural outcomes that might be of dual-use interest, what circuits might be affected and what receptors could be involved in producing these behaviours.[44]

An example of work funded by the BRAIN initiative on receptors that could be of dual-use interest is a paper[45] titled "New Technologies for Elucidating Opioid Receptor Function". Further detailed work on opioid receptor functions include, for example, a publication[46] examining modulation of thalamo-cortico-striatal circuits of the brain in pain processing and reward learning which is obviously of interest in helping to deal with addiction and difficulties in managing pain in human beings. Although both of these opioid receptor studies were undertaken with apparently benign objectives, these same receptors are those that can be attacked by fentanyl and related agents that are certainly of current concern as potential CNS-acting chemical weapons. Such concern has been articulated by the US during ongoing discussions within the OPCW and has also been

[44] Dando, M. R. (2020) *Neuroscience and the Problem of Dual Use: Neuroethics in the New Brain Projects*. Springer Nature, Switzerland. (See Chapter 6: The US Brain Initiative pp. 95–114).

[45] Bruchas, M. R. amd Roth, B. L. (2016) *New Technologies for Elucidating Opioid Receptor Function*. *Trends in the Pharmacological Sciences*, **37**(4), 279–289.

[46] Birdsong, W. T. et al. (2019) Synapse-specific opioid modulation of thalamo-cortico-striatal circuits. *Elife*, **8**:e45146. Doi:10.7554/eLife.45146.

acknowledged, for example, by the US DoD through its Solicitation for a "Wearable medical device to diagnose in-theatre opioid intoxication of the warfighter" in 2018.[47]

Work on circuits underlying the sleep/wake cycle and arousal mechanisms that could be of dual-use interest include a paper[48] on the neuropeptide hypocretin (also known as orexin), the loss of which is a cause of narcolepsy. The paper examined the role of this neuropeptide as a hub for arousal and motivation. In a remarkably short period of time since the neuropeptide was discovered in the late 1990s, its crucial role in numerous important functions such as the stabilisation of the waking state has been elucidated, and this has led, for example, to the development of a specific drug to help people suffering from insomnia. However, understanding how the debilitating disease of narcolepsy is caused could obviously also be of interest to those with malign intentions. Another paper examined how rhythms of the sleeping brain can affect the formation of memory.[49] Again this work has obvious interest in developing our understanding of the cognitive benefits of sleep, but further understanding of the mechanisms of memory formation could also be misused in the future.

Similarly, it is not difficult to find projects funded by the BRAIN initiative that are concerned with the circuits underlying more complex behaviour such as anxiety.[50] Whilst better understanding of such circuits should eventually help the many people who suffer from a range of anxiety disorders, it also might be misused to find ways of causing such disorders. Likewise, detailed investigations of key structures within such circuits like the amygdala[51] and the LC[52] could aid the development of the means to alleviate suffering from overactive fear processing in post-traumatic stress

[47] Department of Defense (2018) *Wearable medical device to diagnose in-theatre opioid intoxication of the warfighter*. SBIR Solicitation. https://sbir.gov/sbirsearch/detail/1508759.

[48] Tyree, S. M. (2018) Hypocretin as a Hub for Arousal and Motivation. *Frontiers in Neurology*, **9**, Article 413; doi:10.3389/fneur.2018.00413.

[49] Puentes-Mestril, C. et al. (2019) How rhythms of the sleeping brain tune memory and synaptic plasticity. *Sleep*, 1–14; doi 10.1093/sleep/zsz095.

[50] BRAIN Initiative Project Number 1U01MH109104-01, Genetic Tools and Imaging Technology for Mapping Cholinergic Engrams of Anxiety.

[51] Ahrens, S. et al. (2018) A Central Extended Amygdala Circuit that Modulates Anxiety. *Journal of Neuroscience*, **38**(24), 5567–5583.

[52] Breton-Provencher, V. et al. (2019) Active control of arousal by a locus coeruleus GABAergic circuit. *Nature Neuroscience*, **22**(2), 218–228.

disorder (PTSD), given the amygdala's role in such processing and the LC's role in arousal, but such knowledge could also be misused to induce fear.

All of this work may be perfectly benign and peacefully orientated, but the fact that a large proportion of the funding for the work comes from the DoD and DARPA could well raise legitimate dual-use questions and also give rise to potential misperceptions which need to be acknowledged and addressed. More broadly the risks of potential malign application of such dual-use research, including in relation to ICA/CNS-acting weapons development, need to be carefully assessed and mitigated against.

8.2.7 The US Rejection of ICA/CNS-Acting Weapons Development

In April 2013, at the Third Chemical Weapons Convention (CWC) Review Conference, the US Acting Under Secretary for Arms Control and International Security, Ms Rose Gottemoeller, clarified that the US considered that: "the development, production, acquisition, stockpiling, or use of incapacitating chemical agents—or any other toxic chemicals—in types and quantities inconsistent with purposes not prohibited by the Chemical Weapons Convention, is clearly prohibited by Article I of the Convention."[53] Ms Gottemoeller highlighted concerns that "illicit programmes could possibly be concealed under the guise of a legitimate treaty purpose, such as law enforcement" and further warned that States Parties "must all be vigilant to ensure that incapacitating chemical agents and other technologies do not jeopardise the twin goals of the Convention—the destruction of all chemical weapons and the prevention of the re-emergence of chemical weapons."[54] Furthermore, in a statement to the OPCW Executive Council meeting held in May 2013, the US Ambassador Dr Robert Mikulak confirmed "very clearly and directly… that the United States is not developing, producing, stockpiling, or using incapacitating

[53] Gottemoeller, R. E. (2013) United States of America: *Statement of Rose. E. Gottemoeller, Acting Under Secretary for Arms Control and International Security, at the Third Review Conference*, RC-3/NAT.45. OPCW, The Hague, 9th April. p. 3.

[54] Gottemoeller, R. E. (2013) ibid.

chemical agents."[55] This position was subsequently reiterated by US officials in 2013 and 2014.[56]

The repeated renunciation by the US of ICA/CNS weapons was a highly significant development. It appears from Ms Gottemoeller's statement which covered "incapacitating chemical agents—or any other toxic chemicals" that the US renunciation would prohibit development, production, and use of toxins and bioregulators intended as ICA weapons. The authors requested clarification from the US regarding the scope of the unilateral US ICA/CNS weapon prohibition and whether it is still maintained. In its 9 November 2021 response, the US confirmed that it "is not developing, producing, stockpiling, or using pharmaceutical-based agents. Accordingly, the United States maintains that this issue is of significant concern".[57] The US however did not clarify whether renunciation extended to toxin and bioregulator-based ICA/CNS-acting weapons.

Further and public clarification of the nature, scope and continuing application of the US position on ICA (or CNS-acting) weapons is important given doubts raised by other CWC States Parties. For example, in its 2021 paper on CNS-acting chemicals submitted to the OPCW Executive Council,[58] the Russian Federation claimed: "[S]ince 2013, the United States has officially stated at various levels and forums—including at the OPCW—that it does not develop, produce, stockpile, or use 'incapacitating' chemicals. However, it can be noted that the development of such chemicals has not stopped."

In addition to its unilateral action, the US has also been at the forefront of the growing group of CWC States Parties advocating that the OPCW address aerosolised CNS-acting chemicals used for law enforcement. On 11 March 2021, the OPCW Executive Council adopted a Decision that

[55] Ambassador Robert P. Mikulak (2013) *United States of America*: *Statement at the Executive Council*, EC-72/NAT.8. OPCW, The Hague. 6th May. p. 2.

[56] See correspondence to Dr M.Crowley, BNLWRP, from Mr K. D. Ward, Executive Director, U.S. National Authority for the Chemical Weapons Convention, Bureau of Arms Control, Verification and Compliance, U.S. Department of State, 30th July 2014, as cited in Crowley, M. and Dando M. R. (2014) op. cit. p. 71.

[57] Gross, L. Executive Director, U.S. Department of State Bureau of Arms Control, Verification and Compliance, U.S. National Authority for the Chemical Weapons Convention, NACS #202 \058 (2021) Response to an information request from the University of Bradford, 9 November 2021.

[58] Russian Federation (2021) *Questions and Answers Regarding the Proposal to Prohibit the Aerosolised Use of Central Nervous System-Acting Chemicals for Law Enforcement Purposes.* EC-96/NAT.6. OPCW, The Hague, 5 March. p. 7.

"[R]ecommend[ed] that the Conference at its Twenty-Sixth Session decide that the aerosolised use of CNS-acting chemicals is understood to be inconsistent with law enforcement purposes as a 'purpose not prohibited' under the Convention."[59]

On 1 December 2021, the 26th Conference of States Parties to the CWC (CSP-26) adopted a landmark Decision to effectively outlaw the aerosolised use of CNS-acting chemical agents for law enforcement purposes. The Decision also noted that "munitions and devices specifically designed to cause death or other harm" through the release of aerosolised CNS-acting chemicals would "constitute a 'chemical weapon'",[60] and consequently should be declared and verifiably destroyed.

Neither a definition of "CNS-acting chemicals" nor the scope of toxic chemicals covered were included in either the Executive Council Decision or in the subsequent CSP Decision. The current authors have requested clarification from the US on its position on these issues and specifically whether it considers that the development, production, and use for law enforcement of aerosolised toxins, bioregulators, and other biologically active peptides should be prohibited under the CWC. Unfortunately, these questions were not addressed by the US in its 9 November 2021 response.[61]

8.3 Research and Development of Malodorants and Associated Means of Delivery

From the late 1940s onwards, US defence and defence-funded projects researched malodorants.[62] In 1966, for example, under Project AGILE, the Battelle Memorial Institute was commissioned by the Advanced Research Projects Agency (ARPA) to study malodorants that could

[59] Executive Council (2021) *Decision: Understanding regarding the aerosolised use of central nervous system-acting chemicals for law enforcement purposes*, EC-96/DEC.7. OPCW, The Hague, 11 March.

[60] Conference of States Parties (2021) *Decision: Understanding regarding the aersolised use of central nervous system-acting-chemicals for law enforcement purposes*, C-26/DEC.10. OPCW, The Hague, 1 December. p. 2.

[61] Gross, L. (2021) op. cit.

[62] Sunshine Project (2001) *Non-Lethal Weapons Research in the US: Calmatives and Malodorants.* Backgrounder 8, July; Sutherland, R. (2008) *Chemical and Biochemical Non-lethal Weapons, Political and Technical Aspects.* SIPRI Policy Paper 23, SIPRI, Stockholm, November; Davison, N. (2009) op. cit. p. 27.

potentially be used in the Vietnam War.[63] This included "determin[ing] whether intercultural differences in olfaction exist…[and]…to what extent they can be utilized in psychological warfare."[64] US defence malodorant research continued after the coming into force of the BTWC and CWC. Whilst limited information is available on the identity of the malodorants investigated, they appear to have included both naturally occurring substances and synthetic chemicals.[65] In its 1999 Annual Report, the Joint Non-lethal Weapons Program (JNLWP) stated that it was sponsoring a project that "investigates odorants and their effects on behavior. It can be used for riot control, to clear facilities, to deny an area, or as a taggant."[66] In 2000, the US Army's Edgewood Chemical Biological Center (ECBC) reported on its research into a range of candidate odours including "US Government Standard Bathroom Odor, butyric acid, vomit odour, sewage odour".[67] However, in 2001, the Nonlethal Environmental Evaluation and Remediation (NEER) Centre at Kansas State University highlighted the "acute health effects" that can be caused by "chemical components" of certain substances considered as potential malodorants.[68]

The US military also undertook or funded projects to develop a variety of delivery and dispersal mechanisms; some intended solely to carry malodorants, whilst others could carry a range of potential payloads which specifically included malodorants.[69] In 1999, the Joint Non-Lethal Weapons Directorate (JNLWD) began funding a project, managed by the US Army's Armament Research, Development and Engineering Center

[63] Bunker, R. J. (1995) *Non-Lethal Weapons: Terms and References*, INSS Occasional Paper 15, USAF Institute for National Security Studies, USAF Academy, Colorado, available at: https://web.archive.org/web/20000824113055/http://www.usafa.af.mil/inss/ocp15.htm (accessed 17 February 2022).

[64] Albert, S. and Hitt, W. (1966) *Intercultural Differences in Olfaction*. Remote Area Conflict Information Center, Battelle Memorial Institute, 2 May, as cited by Sunshine Project (July 2001), op. cit. p. 4.

[65] Sutherland, R. (2008) op. cit. p. 10.

[66] Sunshine Project (2001) op. cit., p. 3.

[67] Bickford, I. et al. (2000) *Odorous Substances for Non-Lethal Application*. Presentation at NDIA Non-Lethal Defense IV, Tysons Corner, Virginia, 20–22 March.

[68] Boguski, T. et al. (2001) *Environmental Issues Associated with Malodorants*. Presentation to the Non-lethal Technology and Academic Research Symposium, Kansas State University, 9 November.

[69] Davison, N. (2009) op. cit. pp. 129, 131–133; Hymes, K. (2009) *Non-lethal weapons in Escalation of Force*. Proceedings of the 5th European Symposium on Non-Lethal Weapons, Ettlingen, Germany, 11–13 May, slide 11; Hambling, D. (2012) US Military Malodorant Missiles Kick Up a Stink. *New Scientist*, Issue 2867, 4 June.

(ARDEC), to develop a delivery system incorporating an 81 mm "non-lethal" mortar munition (NLMM). Work was reportedly carried out by the Army Research Laboratory (ARL), United Defense, and ECBC.[70] The project's goal was the development of a delivery system utilising a mortar munition that could deliver a solid, liquid, aerosol, or powder payload from 200 metres up to 2.5 kilometres from the target with a casing that would not cause injury through kinetic impact on those targeted[71] and that had an effective area of coverage greater than 25 m^2.[72] The munition was based upon the M853A1 81 mm illumination mortar and was intended to be fired from the existing 81 mm M252 mortar system.[73] Potential payloads for this cargo munition included pyrotechnic submunitions (e.g., tear gas), malodorants, and a liquid dispenser.[74] According to a US Army October 2003 presentation, "[E]CBC has begun Artillery/Mortar Malodorant Payload Study".[75] According to information provided by the developers in April 2005, the munition had undergone ballistic firings in which it "successfully deployed payload" and also achieved a range of greater than 2.5 kilometres.[76] Though it appears that a RCA simulant payload[77] was used in the test firings, a range of "possible MoCaP [Mortar

[70] US Army, Joint Non-Lethal Weapons Directorate (2000) *1QFY01 Director's Reviews. Joint RDT&E Pre-Milestone 0 & Concept Exploration Program: 81mm Non-Lethal Mortar*. Picatinny Arsenal, NJ: US Army TACOM/ARDEC-PSAC Center, 20 November. Available at http://www.sunshine-project.org/incapacitants/jnlwdpdf/jnlwdmort.pdf. (last accessed 14th February 2013, link no longer available); Hegarty, R. (2003) *Joint Non-Lethal Weapons Program: Non-Lethal Mortar Cartridge (NLMC)*. US Army Picatinny Arsenal, October.

[71] Evangelisti, M. (2002) *Delivery of Non-Lethal Mortar Payloads by Mortar Systems*. Joint RDT&E Pre-Milestone A Program. Presentation to the 2002 International Infantry & Joint Services Small Arms Systems Section Symposium, National Defense Industrial Association (NDIA), US, 13th–16th May. As cited by Davison, N. and Lewer, N (2003) Bradford Non-Lethal Weapons Research Project (BNLWRP) Research Report No. 4, p. 26.

[72] Hegarty, R. (2003) op. cit., slide 18.

[73] Han, S. et al. (2005) *The 81mm non-lethal mortar carrier projectile*. US Army RDECOM-ARDEC, 40th Annual Armament Systems, 28th April. Available at www.dtic.mil/ndia/2005garm/thursday/han.pdf. (Accessed 28 June 2022), pp. 7 and 16.

[74] Lyon, D. et al. (2000) *Design and Development of an 81mm Non-Lethal Mortar Cartridge*. Presentation to Non-Lethal Defense IV, National Defense Industrial Association (NDIA), US, 20th–22nd March. p. 17.

[75] Hegarty, R. (2003) op. cit.

[76] Han, S. et al. (2005) op. cit. p. 16.

[77] Garner, J. and Lyon, D. (2003) *Proof of Principle for an 81mm Non-Lethal Mortar Cartridge*, Proceedings of the 2nd European Symposium on Non-Lethal Weapons Ettlingen, Germany, 13–14 May. V10. Pfinztal, Fraunhofer, ICT, as cited by Davison, N. and Lewer, N. (2003) op. cit. p. 26.

Carrier Projectile] variants" were highlighted including a "malodorant" payload.[78] Development of the cargo munition—now called the Non-Lethal Indirect Fire Munition (IDFM)—has continued, but no further work on a malodorant payload has been reported. The current version of the IDFM, which contains 14 flashbang submunitions,[79] underwent test firings in July 2018.[80]

From 2004, the US company General Dynamics Ordnance and Tactical Systems worked under the direction of ARDEC to develop a 155mm artillery projectile.[81] The XM1063 was designed to carry out three interrelated functions, to: "separate combatants from non-combatants; suppress, disperse or engage personnel [and] deny personnel access to, use of, or movement through a particular area, point or facility."[82] The XM1063 was intended to have a range of at least 20 kilometres, and potentially up to 28 kilometres.[83] The multiple submunitions would be released above the target and then fall to the ground, dispersing their payloads,[84] with an

[78] Han, S. et al. (2005) op. cit. p. 17.

[79] Joint Non-Lethal Weapons Program (2015) *81 mm Non-Lethal Indirect Fire Munition (IDFM)*. 24 August. Available at https://jnlwp.defense.gov/Portals/50/Documents/Developing_Non-Lethal_Weapons/IDFM%20Trifold_24Aug2015.pdf; Poindexter, L. (2017) *Picatinny engineers granted patent for Indirect Fire Munition Non-Lethal Cargo Carrier Mortar*. Picatinny Arsenal Public Affairs, 2 March. Available at https://www.army.mil/Article/183531/picatinny_engineers_granted_patent_for_indirect_fire_munition_non_lethal_cargo_carrier_mortar.

[80] Cox, M. (2019) Marines Test Nonlethal Mortar Round for Crowd Control. *Military.com*, 19 September.

[81] United States Army (2004) *Picatinny Centre, Non-Lethal Artillery Structural Firing (FYO4) Purchase Order Contract in Support of the FY04 155mm Non-Lethal Artillery Projectile Program*. Contract Number W15QKN-04-M-0328, 14th September. Available at www.sunshine-project.org/incapacitants/jnlwdpdf/XM1063.pdf. (accessed 14th February 2013); McCormick, J. and Lee, R. (2007) *Presentation on 155mm XM1063 Non-Lethal Personnel Suppression Projectile, General Dynamics OTS*. National Defense Industrial Association, 42nd Annual Armament Systems: Gun and Missile Systems Conference and Exhibition. Charlotte, North Carolina, USA. Available at http://www.dtic.mil/ndia/2007gun_missile/GMTuePM2/McCormickPresentation.pdf. (accessed 28 June 2022), p. 4.

[82] McCormick, J. and Lee, R. (2007) op. cit. p. 4.

[83] McCormick, J. and Lee, R. (2006) *155mm XM1063 Non-Lethal Personnel Suppression Projectile*. Presentation to the 41st Annual Armament Systems: Guns and Missile Systems, Conference & Exhibition, National Defense Industrial Association (NDIA), Sacramento, US, 27th–30th March. Available at http://www.dtic.mil/ndia/2006garm/tuesday/mccormick.pdf. (accessed 28 June 2022). p. 12.

[84] McCormick, J. and Lee, R. (2006) op. cit. p. 5.

estimated area coverage of at least 5000 square metres[85]. The proposed payload was described as a "liquid payload"[86] and a "non-lethal personnel suppression agent."[87] Payload agent effectiveness was apparently tested at ECBC,[88] suggesting a chemical fill. A JNLWD reference book on "non-lethal" weapons included a reference to a legal review conducted in 2007 of the "XM1063 Malodorant155mm Artillery Round"[89] that indicated that such malodorant agents were considered for this munition. The project was reportedly suspended in 2008.[90] In a 2012 *New Scientist* article, Hambling noted that although "the project is on hold, [it] has been developed by General Dyanmics…to the stage of test firings and could be reactivated."[91]

In July 2011, the JNLWP issued a Broad Agency Announcement (BAA), soliciting proposals from industry to "develop a non-lethal malodorant weapon which can be dispersed from a 40mm delivered munition (fired from standard 40mm launcher) or a hand-thrown munition."[92] According to the BAA "[T]he Department of Defense (DoD) has developed and tested a malodorant payload, potentially capable of repelling

[85] *NLOS-C Non-Lethal Personnel Suppression*, US Army ARDEC brochure, 2005, as cited in Davison, N. (2007) op. cit. p. 34.

[86] US Army AEDEC (2004) *Solicitation, R—155mm XM1063 Non-lethal Artillery Engineering Support Contract.* Solicitation number: W15QKN-04-X-0819, 30th September. As cited by Davison, N. (2007) *"Off the Rocker" and "On the Floor": The Continued Development of Biochemical Incapacitating Weapons.* Bradford Disarmament Research Centre, Report, No. 8. p. 34.

[87] McCormick, J. and Lee, R. (2006) op. cit. p. 7.

[88] US Army ARDEC (2004) Solicitation (Modification) R-155mm XM1063 Non-lethal Artillery Engineering Support Contract (Ref: W15QKN-04-X-0819). FBO Daily, 30th September 2004, as cited in Davison, N. (2007) op. cit. p. 34.

[89] Joint Non-Lethal Weapons Directorate, *Non-Lethal Weapons (NLW) Reference Book*, 30th June 2011. Copy of report available at http://publicintelligence.net/dod-non-lethal-weapons-2011/. (accessed 28 June 2022), p. viii.

[90] Hambling, D. (2012) US military malodorant missiles kick up a stink, *New Scientist*, issue 2867, 4th June.

[91] Hambling, D. (2012) op. cit.

[92] US Army, JNLWP (2011) *Encapsulation and Delivery of Non-Lethal Malodorant in a 40mm-munition or Hand-thrown Grenade.* Broad Agency Announcement, Solicitation 2011.3, Topic Number: N113-174, Fiscal year 2011, 28 July. Available at https://www.sbir.gov/content/encapsulation-and-delivery-non-lethal-malodorant-40mm-munition-or-hand-thrown-grenade.

humans at concentrations that do not cause trigeminal nerve activation." However, "previous attempts to seal this payload into a tactical form-factor, such as a hand-thrown grenade or 40mm-muntion have not been successful as the chemical composition is highly volatile." Consequently, as part of the BAA project "[A] malodorant weapon could…be created by two means: 1) Developing a sealing or encapsulation technique capable of preventing leaks of the government developed malodorous payload 2) Developing a new malodorous payload." According to the BAA, "[T]his technology could be used by any branch of the military or by civilian forces to deny, move, or suppress personnel." An important requirement for this research was that "[M]alodorous payloads must be effective at repelling humans, while being maintained at concentrations that do not trigger trigeminal nerve activation. Above the concentration threshold of trigeminal nerve activation, chemicals must be classified as Riot Control Agents per the Chemical Weapons Convention."[93]

In June 2014, the US Office of Naval Research and JNLWP issued a BAA, soliciting proposals for research into a range of "non-lethal" technologies, including malodorants for fiscal year 2015. It is notable that under this solicitation—in wording similar to the 2011 BAA—research "shall be limited to non-lethal malodorants that are not considered riot control agents, i.e., the malodorant must not cause 'sensory irritation' or any 'disabling physical effects' ".[94] The objective of these malodorants was to "cause immediate repel effects to humans in open and confined spaces" and it was noted that "[the] effect [of which] can last 24 hours or more".[95] One part of this BAA highlighted "[A]dvanced Non-Lethal Technologies that Move/Suppress/Deny/Disable through Combine[d] NL[non-lethal] Effects on Individuals and Crowds". Here the BAA stated that "[A]ll non-lethal stimuli shall be considered, individually and in combination to elicit combined non-lethal effects" and that "[R]elevant non-lethal stimuli would be combinations of forms [including]…non-irritating malodorants." The ultimate goal or "end-state" of this part of the BAA "would be

[93] US Army, JNLWP (2011) op. cit.

[94] US Office of Naval Research, JNLWP (2014) *Fiscal Year 2015 Non-Lethal Weapons Technologies Broad Agency Announcement*, ONRBAA14-008. 5 June, p. 6.

[95] US Office of Naval Research, JNLWP (2014) op. cit. p. 7.

the development of a hand held combined effects non-lethal weapon which addresses the needs to move/suppress/deny/disable." According to the BAA, "[T]his includes, but is not limited to, the ability to: (1) defeat snipers; (2) engage neutral and non-hostile crowds using non-lethal means; (3) defeat raids and perform route reconnaissance; and (4) assist in convoy protection, point defense, vehicle/vessel stopping and force protection missions."[96]

In February 2021, the Department of the Navy Small Business Innovation Research (SBIR) Program launched a BAA soliciting proposals to facilitate the development of "a suite of more compact and lightweight long range non-lethal counter-personnel and counter-materiel payloads for integration on small tactical vehicles/platforms and UxS [unmanned systems]."[97] These "Intermediate Force Capabilities [IFC]" payloads were intended to "support a variety of stabilization operations, gray zone warfare, and regular and irregular warfare missions across the full Range of Military Operations." The scope of potential technologies and payloads that could be explored were intended to be broad. Among those highlighted were "*12 gauge/40mm non-lethal munitions* (blunt impact, flash-bang, riot control agents, human electro-muscular incapacitation, *malodorant*) *with associated munition launching/targeting and fire control systems* (Emphasis added)."[98] No further details are publicly available regarding whether, and if so what, malodorant research and development activities were undertaken to fulfil the 2011, 2014 or 2021 BAA solicitations.

Certain US companies have promoted malodorant weapons to US and or foreign law enforcement or military. For example, until at least January 2022, Mistral Inc., marketed the malodorant Skunk which it has described as an "organic solution developed in conjunction with police forces of [unnamed] allied countries."[99] It is "designed to meet the operational

[96] US Office of Naval Research, JNLWP (2014) op cit. p. 37.

[97] US Department of the Navy,(2021) *Small Business Innovation Research Program*, SBIR 21.1 Program Broad Agency Announcement, Version 9, N211-001. 26 February, p. 15.

[98] US Department of the Navy, Small Business Innovation Research Program, (2021) op. cit. p. 15.

[99] Mistral Inc. (undated) *Skunk malodorant systems for crowd control*, FINAL—MSI Skunk Product Brochure 5.16.13.pdf (mistralsecurityinc.com) (accessed 28 January 2022, subsequently removed).

requirements of law enforcement, and military agencies that are challenged with interdicting during demonstrations or passive civil disobedience." According to Mistral Inc., Skunk is a "harmless deterrent consist[ing] of an extremely foul-smelling liquid, with the viscosity of water". It can be "sprayed over a large area using a standard water cannon, or launched in less-lethal type munitions to achieve greater distance and a combination effect." The company has also promoted a range of attendant delivery systems, including a 60 oz. canister, 40 mm "less lethal" grenade, and a "skid sprayer" with a 50 gallon tank that has a range of over 60 feet and dispenses Skunk at a rate of 7 gallons per minute. According to the company, "[S]kunk can be purchased in 264 gallon barrels and used with pumper trucks to treat large areas in a very short period of time."[100] According to the British Broadcasting Corporation (BBC), "[S]everal US police departments, including the St Louis Metropolitan Police, are reported to have bought it."[101] Whilst Mistral Inc. does not identify which "police forces of allied countries" it worked with to develop Skunk, an apparently very similar if not identical product also called "Skunk" has been developed by the Technological Development Department of the Israel Police and the Israeli company Odortec Ltd.[102] According to the BBC, an Israeli Defence Forces (IDF) spokesperson claimed Skunk to be "an effective, non-lethal, riot dispersal means" that can reduce the risk of casualties, whilst the Israeli police have described it as a "humane" option.[103] International and Israeli human rights organisations and media have reported the repeated excessive and wide area use of Skunk by the IDF and Israeli police, predominately against Palestinian communities;

[100] Mistral Inc. (undated) *Crowd Control—Skunk*.https://www.mistralsecurityinc.com/Our-Products/Skunk/Crowd-Control (accessed 28 January 2022); Mistral Inc. (undated) *Skunk Malodorant Systems For Crowd Control*, Final—Skunk Product Brochure 4.13.2015.pdf (mistralinc.com) (accessed 28 January 2022, subsequently removed).

[101] BBC News (2015) *Who, What, Why: What is skunk water?*, 12 September. Available at https://www.bbc.co.uk/news/magazine-34227609. For further details, including invoices, of the St Louis Police acquisition see: Tucker, P. (2015) *After Ferguson Unrest, St. Louis Police Bought Stink Weapons to Launch at Protesters*, 11 August. Available at https://www.defenseone.com/technology/2015/08/after-ferguson-unrest-st-louis-police-bought-stink-weapons-launch-protesters/119044/ (accessed 3 February 2022).

[102] For details of Odortec's Skunk including Material Safety Data Sheet see company website archived on Wayback machine https://web.archive.org/web/20110313032551/http://www.skunk-skunk.com/ (accessed 3 February 2022). For further discussion see Crowley, M. (November 2016) op. cit. pp. 45–46.

[103] BBC News (2015) op. cit.

and in some cases it is claimed to have caused deleterious health effects.[104] To date, there have been no confirmed reports of the employment of malodorant weapons by US police, security or military forces.

8.3.1 US Application of the CWC to Malodorants

The US military has given some, albeit conflicting, indications of how it has applied the CWC with regards to malodorants. In 1997, a preliminary legal review of "chemical based nonlethal weapons" by the US Navy's office of the Judge Advocate General (JAG) argued that malodorant chemicals were not restricted by the CWC because they did not rely on their toxic properties to exert their effects.[105] Subsequently, a 2003 NLW science and technology assessment by the National Research Council for the JNLWD and the Office of Naval Research, found that "[M]alodorants…are not considered toxic chemicals…[and] have a strong potential for controlling crowds, clearing facilities, and area denial."[106] This legal interpretation appears to have subsequently been either modified or replaced.

In a June 2012 *New Scientist* article, Kelly Hughes, spokesperson for the JNLWP, stated that "the CWC prohibits some temporarily disabling compounds on the basis of whether they activate the trigeminal nerve when people are exposed to it—those that do are classed as riot-control

[104] See for example: Michaeli, S. (2013) Crowd Control Israel's Use of Crowd Control Weapons in the West Bank, B'Tselem [The Israeli Information Center for Human Rights in the Occupied Territories], January. Available at http://www.btselem.org/download/201212_crowd_control_eng.pdf; Association for Civil Rights in Israel(2013) *Spraying "skunk" at homes—violation of the right to dignity and freedom of demonstration*. ACRI, 23rd January [original in Hebrew], https://www.acri.org.il/he/25560; Amnesty International (2014) *Israel and Occupied Palestinian Territories: Trigger-happy: Israel's Use of Excessive Force in the West Bank*. MDE 15/002/2014, 27th February; The Economist (2015) *A whiff from hell: Skunk, a high-tec Israeli weapon against stone-throwers*, 6th June; BBC (2015) op. cit.; Physicians for Human Rights/International Network of Civil Liberties Organisations (2016) *Lethal in Disguise: The health consequences of crowd control weapons*. https://www.inclo.net/pdf/lethal-in-disguise.pdf.

[105] US Navy (1997) *Preliminary Legal Review of Proposed Chemical-Based Nonlethal Weapons, Department of the Navy*, Office of the Judge Advocate General, International & Operational Law Division, as cited by Davison, N. (2009) op. cit. p. 67.

[106] National Research Council (2003) *An Assessment of Non-lethal Weapons Science and Technology*, National Academies Press, Washington D.C., p. 81.

agents (RCA). The nerve conveys sensation from the face, cheeks and jaw, but does not control smell."[107] Consequently, according to Hughes, "[I]f a particular malodorant is disseminated with a concentration that does not activate the trigeminal nerve, it may not require designation as an RCA under the CWC."[108] This JNLWP treaty interpretation is questionable, firstly because the CWC does not define RCAs in relation to whether they activate the trigeminal nerve, and secondly because RCAs are regulated not prohibited under the CWC—it is only their use as a "method of warfare" which is expressly prohibited under the Convention. It appears, however, that this interpretation has informed both the July 2011 and the June 2014 JNLWP BAA solicitations discussed earlier. An indication that this interpretation may continue is found in the JNLWRP Science and Technology Strategic Plan covering 2016–2025, where "[N]on-irritating malodorants" are included under "[C]ounter-Personnel Capability and Technology" as an area for "future potential investment".[109] Consequently, it appears that the US military does not consider at least certain malodorants to be RCAs and has been exploring development of such malodorant weapons, raising concerns of their possible intention to employ such weapons in armed conflict environments, which in certain circumstances may potentially breach Article I.5 and/or Article II.1 of the CWC. The US does not appear to have provided a public statement whether, and if so how, it considers malodorants are regulated under the BTWC.

8.4 Research and Development of Riot Control Agent Means of Delivery

Numerous US commercial companies and certain US State entities have researched and developed a range of riot control agent (RCA) means of delivery—including some which disseminate oleoresin capsicum (OC), a sensory irritant of biological origin, and/or pelargonic acid vanillylamide (PAVA), a synthetic analogue—in limited quantities and over relatively

[107] Hambling D. (2012) op. cit., p. 1.
[108] Hambling D. (2012) op. cit., p. 1.
[109] United States (2016) *Joint Non-Lethal Weapons Program, Strategic Plan 2016–2025.* Science and Technology, Department of Defense, p. 27.

small areas.[110] US commercial OC/PAVA products are marketed to US police and military forces, primarily for crowd control and other law enforcement activities; for civilian self-defence and also for export. If used in appropriate amounts and circumstances, they would appear to be consistent with the BTWC and CWC.[111]

However, certain OC/PAVA weapons acquisitions by US military forces do raise potential concerns. The US company Pepperball has developed "less lethal" launchers and projectiles including 0.68 calibre projectiles containing oleoresin capsicum/PAVA powder or CS powder. These frangible irritant projectiles "burst upon impact, producing a strong kinetic impact and leaving a debilitating cloud that affects the eyes, nose and respiratory system".[112] Pepperball products are promoted to the US and foreign law enforcement and military communities. In June 2018, the US Army awarded Pepperball a $650,000 contract for 267 units of its Variable Kinetic System (VKS) long-range, semi-automatic, non-lethal launcher to "support soldiers with non-lethal force protection measures when out in the field". This decision was in support of US Forces-Afghanistan (USFOR-A) Joint Force Protection Directorate. Whilst the launchers were delivered and subsequently used in training, there have been no reports of their use in Afghanistan or elsewhere, to date. According to the JNLWP, "[T]he VKS is designed to deny access into/out of an area

[110] U.S. DoD Non-Lethal Weapons Program, Joint Intermediate Force Capabilities Office, *Oleoresin Capsicum Dispensers.* Available at https://jnlwp.defense.gov/Current-Intermediate-Force-Capabilities/Oleoresin-Capsicum-Dispensers/; United States DOD, JNLWP (2012) *Non-Lethal Weapons (NLW) Reference Book.* pp. 3 and 6. Available at https://www.supremecourt.gov/opinions/URLs_Cited/OT2015/14-10078/14-10078-3.pdf.

[111] There have been numerous reports of excessive or inappropriate use of unidentified 'limited area' OC means of delivery by US law enforcement officials. Such practice appears to contravene relevant human rights law and standards. See for example Human Rights Watch (2020) *"Kettling" Protesters in the Bronx Systemic Police Brutality and Its Costs in the United States*, September; Amnesty International (2020) *USA: The World is Watching, Mass Violations by US Police of Black Lives Matter Protesters' Rights.* AMR 51/2807/2020.

[112] Pepperball (2018) *PepperBall Awarded U.S. Army Contract for Non-Lethal Protection*, 13 June. Available at: https://pepperball.com/pepperball-awarded-u-s-army-contract-for-non-lethal-protection/; Smith, T. (2018) Like hot sauce in your face, the Army's newest non-lethal weapon is spicy! *Army Times*, 15 June. Available at https://www.armytimes.com/news/your-army/2018/06/15/like-hot-sauce-in-your-face-the-armys-newest-non-lethal-weapon-is-spicy/?utm_source=Sailthru&utm_medium=email&utm_campaign=EBB%25206.27.18&utm_term=Editorial%2520-%2520Early%2520Bird%2520Brief.

to individuals, to move individuals through an area, and suppress individuals. The system has the ability to support multiple missions including Force protection, Detainee operations, Crowd control, Defensive and offensive operations."[113] The VKS can be used with either a magazine holding 10–15 projectiles or a hopper holding 180 projectiles. It has a maximum range of 150 feet and can fire 20 plus projectiles per second. The VKS can fire a variety of Pepperball projectiles, including *Live X* rounds holding 2.5g of 5% PAVA powder—the "most potent and powerful concentration"—equivalent to the agent contained in 10 regular Pepperball PAVA rounds.[114] Given the maximum range, rate of fire and PAVA amounts/concentrations of projectiles, soldiers employing the VKS are capable of rapidly blanketing wide areas with irritant, effecting significant numbers of people, which in certain proposed missions would be of potential concern.

Certain US companies and State entities have researched and developed a further range of 'wide area' RCA means of delivery of potential concern that are capable of dispersing riot control agents over large areas or extended distances. They include: large back-pack or tank spray devices; indoor RCA dispersion devices; multi-launchers and associated RCA projectiles; RCA mortar projectiles and other large calibre projectiles; and unmanned ground and aerial vehicles capable of RCA dispersal.[115] For the majority of US RCA 'wide area' dispersal mechanisms identified, the manufacturers, or the US military organisations overseeing the development projects, described their payloads either generically as "riot control agents" or "tear gas", or where a specific RCA was identified it was normally CS. However, a number of delivery mechanisms appear capable of dispersing, or being adapted to disperse other RCAs, potentially including OC and its synthetic analogues.

In certain cases, OC or PAVA have been identified by the manufacturers as the RCA employed or that could be employed in their products. For

[113] United States (undated), *Variable Kinetic System (VKS) Non-Lethal Launcher System Variable Kinetic System (VKS) Non-Lethal Launcher*. Joint Intermediate Force Capabilities Office, Non-Lethal Weapons Program, Department of Defense. Available at https://jnlwp.defense.gov/Current-Intermediate-Force-Capabilities/Variable-Kinetic-System/. (Accessed 7 February 2022).

[114] https://pepperball.com/content/PEP-21006-Round-LIVE-X-SS-120121.pdf.

[115] Crowley, M. (2013) *Drawing the line: regulation of 'wide area' riot control agent delivery mechanisms under the Chemical Weapons Convention*, University of Bradford/Omega Research Foundation, April; Crowley, M.(2015) *Tear gassing by remote control: The development and promotion of remotely operated means of delivering or dispersing riot control agents*, University of Bradford/Omega Research Foundation/Remote Control Project, December.

example, the US company MSI Delivery Systems Inc., previously developed and until at least 2016 promoted the Afterburner 2000 system (AB2K).[116] Company marketing materials described the product as a "robust multimission, multi-purpose smoke generator capable of rapidly blanketing large areas with dense smoke."[117] The standard non-toxic camouflage/training smoke "can be *mixed with irritants such as OC, CS, Pepper* [that] upgrades mission capabilities to include: *Crowd Control and Civil Unrest*, SWAT Teams and Tactical Incursions, *Prison Systems for Riot Control/Prisoner* Extraction), Non-lethal Terrorist Suppression/Repel Prirates, *Military Operations (MOUT/COIN)*"[118] (emphasis added). According to the company, the Afterburner 2000 could release over 1500 cubic feet of smoke with a range greater than 100 feet (30 metres) in one second.[119] The marketing material stated that "[the]standalone version" of the Afterburner 2000 "expels 50,000 cubic feet (1,416 cubic meters) of smoke on a single charge"; whilst the "dependent version with high-capacity backpack expels 320,000 cubic feet (9,061 cubic meters) of smoke on a single charger."[120] Two US companies—NonLethal Technologies, Inc. and Mace Security International, Inc.—as of September 2022, have promoted a fixed installation RCA dispersion device called the TG Guard System which can employ either OC or CS.[121] According to NonLethal Technologies, Inc. the system is designed to provide "critical force protection for personnel and facilities", and has been promoted for use inside prisons[122] and for perimeter protection of "embassies, military

[116] MSI Delivery Systems Inc. (2016) *AB2K MMADS User and Safety Manual.* Third Edition, February 1 Available at: https://dl-manual.com/doc/ab2k-mmads-user-safety-manual-third-edition-0vejljpejnop (Accessed 18 February 2022). At the time of writing the company website was no longer operational.

[117] MSI Delivery Systems Inc. (2016) *op. cit.; MSI Delivery Systems Inc. (2010) Afterburner 2000 Smoke Delivery System, White Paper, 25 January 2010.*

[118] MSI Delivery Systems Inc. (undated) Afterburner 2000 aerosol delivery system, slide-show presentation, slide 6. The company further stated that it only provides the non-toxic training smoke. "Irritants" are purchased [by the customer] from local suppliers. MSI Delivery Systems Inc. (2010) op.cit., p.4.

[119] MSI Delivery Systems Inc. (2010) op. cit. p.3.

[120] Ibid.

[121] NonLethal Technologies, Inc. (2017) Less Lethal, Tactical Munitions and Weapons Systems for Military, Corrections and Law Enforcement, Product catalogue. Available on http://www.nonlethaltechnologies.com/catalog.htm, accessed 6 September 2022; Mace Security International, Inc. (2019), TG Guard Security Protection System, https://tgguard.com/index.html, accessed 6 September 2022.

[122] NonLethal Technologies, Inc. (2017) op.cit. p.11.

bases, courts, and other government installations".[123] When remotely initiated by an operator, the system can "deploy OC irritant dust from strategically positioned squib fired dispensers within, or around perimeters of critical value buildings….to deny access to hostile individuals or crowds attempting to enter such government buildings to destroy or disrupt government operations".[124] The basic TG Guard Control Unit can "operate and discharge up to 25 tear gas Dispensers selectively … [whilst]… larger facilities can use multiple Control Units and Dispensers to accommodate their security needs."[125] Each "Dispenser" can hold and instantaneously dispense 110 grammes of either "CS powder" or "OC irritant dust".[126]

8.4.1 US Application of the CWC and BTWC

While the majority of CWC States Parties hold a comprehensive interpretation of the Convention's Article I.5 prohibiting all military use of RCAs (including OC and PAVA) in armed conflict, the US maintains a long-held position, under Executive Order 11850, that RCAs can be legitimately used *inter alia*: (a) in riot control situations including rioting prisoners of war; (b) where civilians are used to mask or screen attacks; (c) in rescue missions in remote areas, of downed aircrews and passengers, and escaping prisoners; and (d) to protect convoys from civil disturbances, terrorists, and paramilitary organisations.[127] Depending on the circumstances, activities described in (b), (c), and (d) could potentially breach the Convention, and consequently the US position has been of long-standing concern to many CWC States Parties.

The US interpretation of the BTWC in this area is also of potential concern. In 1998, a legal review of OC undertaken by the Office of the US Navy Judge Advocate General (JAG) concluded that: "neither the

[123] NonLethal Technologies, Inc. (2018), Product Data Sheets,TG-100-OC – Irritant Powder Dispenser OC Powder, https://www.nonlethaltechnologies.com/pdf/DS/TG-OC.pdf accessed 6 September 2022.

[124] NonLethal Technologies, Inc. (2018), op.cit.

[125] NonLethal Technologies, Inc. (2017) op.cit. p.11.

[126] NonLethal Technologies, Inc. (2018), Product Data Sheets,TG-100-OC – Irritant Powder Dispenser OC Powder, https://www.nonlethaltechnologies.com/pdf/DS/TG-OC.pdf accessed 6 September 2022.

[127] Ford, G. (1975) *Executive Order 11850—Renunciation of Certain Uses in War of Chemical Herbicides and Riot Control Agents*, 8th April. 40 FR 16187 CGR, 1971–1975 Comp., 980.

1925 Geneva Gas Protocol nor the 1972 Biological Weapons Convention prohibit the acquisition or employment of oleoresin capsicum."[128] Furthermore, the JAG legal review also stated that "OC…falls outside the BWC definition. It is, in fact, used as an additive in foodstuffs and pharmaceutical products."[129] The JAG review is troubling on both counts. Whilst it is clear that neither the Geneva Protocol nor the BTWC would *per se* prohibit the acquisition or employment of OC, the current authors contend that both agreements do constrain the use of this agent, the former prohibiting use as a "method of warfare" and the latter prohibiting development, production, stockpiling, acquisition, or retention of OC for use in "armed conflict" or for "hostile purposes". It should be noted that the US JAG legal review was undertaken in 1998 and it is unclear whether the position outlined is maintained by the current US Administration.

8.5 US Biodefence

8.5.1 Establishing the Boundaries of Biodefence

On 23 December 1975 Brent Scowcroft, the US National Security Advisor, issued a memorandum, detailing policy guidelines for US implementation of the BTWC. According to the Scowcroft Memorandum, biodefence activities permitted under the Convention were limited solely to

> [A]ctivities concerned with the protection of human beings, animals, plants, and matériel from the effects of exposure to microbial or other biological agents or toxins, *including vulnerability studies* and research, development and testing of equipment and devices such as protective masks and clothing, air and water filtration systems, detection, warning and identification devices, and decontamination systems. (Emphasis added)[130]

Whilst the Scowcroft Memorandum specifically authorised "vulnerability studies", it did not expressly authorise "threat assessment" activities that went beyond this, such as the creation of novel pathogens (or indeed

[128] United States, Office of the Judge Advocate General (1998) *Legal Review of Oleoresin Capsicum (OC) Pepper Spray, for Commander, Marine Corps Systems Command.* Ser 103/353, 19th May 1998, Department of the Navy, United States. p. 10.

[129] United States, Office of the Judge Advocate General (1998) op. cit. p. 10.

[130] The Scowcroft Memorandum was reproduced in the *CBW Conventions Bulletin*, **57** in September 2002. (p. 2).

novel toxins), the development of munitions or other delivery mechanisms or the analysis of other weaponisation techniques.[131]

In the first two decades following US ratification of the BTWC, the US Biological Defense Research Program (BDRP) was reportedly conducted in a reasonably open manner. Threat assessment studies and development projects were not classified, and the US Congress received detailed annual reports of such practices to facilitate oversight.[132] However, certain activities falling within the BDRP ambit were highlighted as being of potential concern potentially crossing the line from biodefence to offensive capability.

One example highlighted by Wright and Ketcham in 1990 was a project funded by the Medical Research and Development Command which "aims at the isolation and characterisation of the gene for a protein called Hibernation Induction Trigger or HIT, and the mass production of the protein using genetic engineering. HIT, a substance isolated from the blood of hibernating animals, was shown…in earlier studies to induce a hibernation-like state."[133] Wright and Ketcham suggested that despite claims made for medical applications of HIT, "[I]t is difficult to see how mass production of HIT would contribute to biological defence. Offensive application, on the other hand, seems more likely if delivery of HIT as an active agent is achieved."[134]

8.5.2 Classified Threat Assessment Projects

During the late 1990s, elements of the US biodefence community circumvented transparency and accountability measures, apparently due to increased concerns over the threat of biological and chemical terrorism. The Pentagon and the intelligence community began to conduct secret threat assessment studies that clearly exceeded the limits for defensive research specified in the Scowcroft Memorandum, but Congress was not

[131] Enemark, C. (2006) United States biodefense, international law, and the problem of intent. *Politics and the Life Sciences*, **24**(1–2), 32–42.

[132] Tucker, J. (2004) Biological Threat Assessment: Is the Threat Worse Than the Disease? *Arms Control Today*, **34**(8), 13–19.

[133] Wright, S. and Ketcham, S. (1990) The problem of interpreting the US biological defense research program, in S. Wright (Ed.) *Preventing a Biological Arms Race*. MIT Press, Cambridge, Massachusetts., as cited in Dando, M. R. (1996) *A New Form of Warfare*, Brassey's, London, p. 157.

[134] Wright, S. and Ketcham, S. (1990) op. cit.

informed of the change. During the Clinton administration there was classified biodefence work conducted without the full knowledge of the National Security Council.[135]

In September 2001, a *New York Times* investigation uncovered three classified US biodefence "threat assessment" projects conducted between 1997 and 2001 that skirted if not breached the BTWC.[136] Under Project Clear Vision, Battelle Memorial Institute was reportedly contracted by the Central Intelligence Agency (CIA) to reconstruct and test a Soviet-designed biological cluster bomblet in order to assess its biological agent dissemination characteristics. Under Project Bacchus, the Defense Threat Reduction Agency tested whether terrorists or a 'rogue nation' could construct a sophisticated bioweapon plant from commercially available materials without raising suspicions. Project personnel bought the supplies, built the facility in the Nevada desert, and used it to produce non-pathogenic bacterial spores that were then dried and weaponised. Project Jefferson, which was administered by the Defense Intelligence Agency, was devised to reproduce a genetically modified strain of anthrax bacterium developed by Russian scientists in the early 1990s, with the goal of measuring the strain's resistance to the licensed US anthrax vaccine. It is uncertain whether this last project went beyond the planning stage before its termination. Both Project Clear Vision and Project Bacchus were initiated and completed during the Clinton Administration, whilst Project Jefferson was initiated under Clinton and continued into the Bush administration. Although these three clandestine projects involved pathogens rather than toxins or bioregulators, they illustrate the secretive and controversial nature of previous US biodefence "threat assessment" studies, some of which were of contested legitimacy.

The Bush Administration argued that all three projects were consistent with the BTWC because the underlying intent was defensive.[137] This interpretation has been contested by certain arms control and international

[135] Tucker, J. (2004) op. cit.

[136] Miller, J. et al. (2001) US Germ Warfare Research Pushes Treaty Limits. *New York Times*, 4 September. Available at www.nytimes.com/2001/09/04/world/us-germ-warfare-research-pushes-treaty-limits.html?sec-health; See also Bansak, K. (2011) Biodefense and transparency. *The Nonproliferation Review*, **18**(2), 349–368; Enemark, C. (2006) op. cit.; Wheelis, M. and Dando, M. R. (2003) Back to Bioweapons? *Bulletin of the Atomic Scientists*, January/February. Available at https://journals.sagepub.com/doi/pdf/10.2968/059001013; Tucker, J. (2004) op. cit.

[137] Ruppe, D. (2004) Proposed U.S. Biological Research Could Challenge Treaty Restrictions, Experts Charge. *Global Security Newswire*, June 30.

legal experts who argued that Project Clear Vision's reconstruction of the Soviet cluster bomblet breached the BTWC Article I prohibition on development, production, stockpiling, acquisition, or retention of "weapons, equipment or means of delivery designed to use [biological] agents or toxins for hostile purposes or in armed conflict." They argued that, whereas the definition of biological agents and toxins in the first paragraph of Article I is purpose based and entails a judgement of intent, the prohibition on munitions and delivery systems in the second paragraph is unconditional. Ambassador Jim Leonard, who had been lead US negotiator of the BTWC, stated that "[P]aragraph one and paragraph two are written differently, and one has to assume that there's a reason for that difference." The obvious reason, he said, is that legitimising the development and production of delivery devices for defensive purposes would enable countries to develop and build the components for an entire weapon in the name of defence. It "makes any kind of policing of the treaty… virtually impossible".[138] Such concerns were apparently raised but overridden during the Clinton Administration's internal project review. According to the *New York Times* investigation, "[A] State Department official argued for a strict reading of the treaty: the ban on acquiring or developing 'weapons' barred states from building even a partial model of a germ bomb, no matter what the rationale. 'A bomb is a bomb is a bomb,' another official said at the time."[139]

In addition to the contested legality of Project Clear Vision, the secret nature under which all three threat assessment projects were undertaken raised broader concerns regarding national oversight, reporting and public transparency of US biodefence activities. Furthermore, a number of BTWC States Parties were disturbed that the US had not formally reported these three projects under its biodefence activities as part of its annual BTWC CBM declarations. A review by the current authors of all subsequent publicly available US CBW declarations from 2001 to 2021 could find no formal reporting by the US of the three classified threat assessment studies, nor were these classified studies formally acknowledged or addressed in publicly available US National Statements to BTWC Meetings of States Parties. Concerns were expressed by Tucker that in justifying the omissions, the Bush administration seemed to imply that the CBM declarations—and, by extension, the BTWC itself—only covered Defense

[138] Ruppe, D. (2004) op. cit.
[139] Miller, J. et al. (2001) op. cit.

Department activities and not those conducted by the CIA and other agencies.[140] The current authors have requested clarification of the scope of US biodefence activities and agencies covered and required to be reported by the US under its annual BTWC CBM declarations. Unfortunately, the 9 November 2021 US response did not address this issue.[141]

BTWC State Parties' concerns regarding oversight, reporting, and transparency of the US biodefence programme were deepened and further politicised by the US government's near-contemporaneous decision in August 2001 to reject the draft text for a BTWC Protocol intended to strengthen the Convention through a system of mandatory declarations and inspections.[142] In addition to rejecting the proposed Protocol text that had been under negotiation by the BTWC States Parties for six years, the US unilaterally withdrew from this negotiation process effectively terminating it. Tucker has contended that "one reason for this decision was the administration's concern that intrusive on-site visits to US biodefense facilities might compromise classified threat-assessment research."[143] Indeed, the 2001 *New York Times* investigation stated that "[A]dministration officials said the need to keep such projects secret was a significant reason behind President Bush's recent rejection of a draft agreement to strengthen the germ-weapons treaty [i.e. the Protocol]."[144]

8.5.3 US National Biodefense Analysis Counter-Measures Center

Following the 9/11 Al-Qaeda terrorist attacks and the subsequent US terrorist anthrax letter attacks, in July 2002, President Bush proposed "the establishment of a National Biological Weapons Analysis Center in the Department of Homeland Security to address relevant medical scientific issues, *to include BW threat and risk assessments* and to determine which countermeasures require priority research and development" (emphasis added).[145] The National Biodefense Analysis and Counter-measures

[140] Tucker, J. (2004) op. cit.
[141] Gross, L. (2021) op. cit.
[142] Enemark, C. (2006) op. cit. Tucker (2004) op. cit.
[143] Tucker, J. (2004) op. cit.
[144] Miller, J. et al. (2001) op. cit.
[145] United States (2002) *National Strategy for Homeland Security*. Office of Homeland Security, July.

Center (NBACC) was subsequently created "to be a national resource to understand the scientific basis of the risks posed by biological threats and to attribute their use in bioterrorism or biocrime events".[146] The NBACC incorporates the National Biological Threat Characterization Center (NBTCC) which according to the US government "conducts studies and laboratory experiments to fill in information gaps to better understand current and future biological threats; to assess vulnerabilities and *conduct risk assessments*; and to determine potential impacts to guide the development of countermeasures such as detectors, drugs, vaccines, and decontamination technologies" (Emphasis added).[147]

Disquiet has been voiced ever since its establishment, that the NBACC, and particularly the NBTCC, may be undertaking activities particularly with regard to risk assessments, that could be in conflict with the BTWC. Of particular concern was a February 2004 presentation, by the NBACC's Deputy Director George Korch in which he described the planned capabilities for the NBTCC as:

> Basic Pathogenesis, Susceptibility to Current Rx, *Aerosol Dynamics, Novel Delivery of Threat, Novel Packaging, Simulation/Modeling (Epidemiology), Genetic Engineering, Environmental Stability, Bioregulators/Immunomodulators*, Assay Development Information Analysis for IC, *Genomics/Proteomics/Transcript, Red Teaming* [i.e. duplication of threat scenarios], Host Range Studies, *Aerosol Animal Model Development*, Support to Strategic National Stockpile (Pharmaceuticals and Biologics). (Emphases added)[148]

In his presentation Korch framed the task areas for biothreat agent (BTA) analysis and technical-threat assessment as "[A]cquire, Grow, Modify,

[146] United States, National Biodefense Analysis and Countermeasures Center website, originally http://www.dhs.gov/files/labs/gc_1166211221830.shtm, subsequently replaced by https://bnbi.org/.

[147] United States Congress (2013), *Department of Homeland Security Appropriations for 2014: Hearings Before a Subcommittee of the Committee on Appropriations.* House of Representatives, 113th Congress, First Session, Part 1, Committee on Appropriations, Subcommittee on Homeland Security, January, U.S. Government Printing Office p. 959.

[148] Korch, G. (2004) *Leading Edge of Biodefense—The National Biodefense Analysis and Countermeasures Center.* Presentation at the DoD Pest Management Workshop, Naval Air Station, Jacksonville, Florida, Feb. Sponsored by the Armed Forces Pest Management Board Office of the Deputy Under Secretary of Defense (Installations and Environment). Department of Defense, Washington, D.C. February 2–13. Slide 12.

Store, Stabilize, Package, Disperse".[149] According to Korch characterisation of "classical, emerging, and genetically engineered pathogens for their BTA potential" would include wet-lab and computer modelling of "aerobiology, aerosol physics, and environmental stability"; computer modelling of "feasibility, methods, and scale of production"; wet-lab and computer modelling of "physical/chemical properties of dissemination and alternatives to aerosol dissemination"; and "Red Team operational scenarios and capabilities assessment."[150]

These proposed activities were strongly criticised by Professor Leitenberg, Ambassador Leonard, and Dr Spertzel. In their opinion:

> Taken together, many of the activities…may constitute development in the guise of threat assessment, and they certainly will be interpreted that way. Development is prohibited by the Biological Weapons Convention. How would these activities differ from their counterparts in the pre-1969 US BW program except for production and stockpiling this time not being envisioned?[151]

These concerns were further exacerbated by the Department of Homeland Security's (DHS) description of the NBACC's programmatic mission. As part of the FY 2006 Congressional Justification for the Department of Homeland Security, the DHS stated that:

> The work in these [NBACC] laboratories will be for defensive purposes only. The…Biological and Toxin Weapons Convention…prohibits the development, production, stockpiling, and acquisition of *offensive* biological weapons. The U.S. is a signatory to this treaty, and all activities performed at the NBACC Facility will comply with this treaty and with all other applicable laws. (Emphasis added)[152]

Leitenberg argued that the insertion of "offensive" in front of "biological weapons" was a "direct contradiction of all existing international legal

[149] Korch, G. (2004) op. cit. *Slide 16.*

[150] Korch, G. (2004) op. cit. *Slide 17.*

[151] Leitenberg, M. et al. (2004) Biodefense crossing the line. *Politics and the Life Sciences*, **22**(2), 2–3. p. 2.

[152] Center for Arms Control and Non-Proliferation (2005) *Fact Sheet: The Biological and Toxin Weapons Convention (BWC) and its Interpretation by the Department of Homeland Security*, April; as cited in Leitenberg, M.(2005) *Assessing the biological weapons and bioterrorism threat*. Strategic Studies Institute, US Army War College, December.

interpretations of Article 1 of the BWC", as it "implie[d] that the BWC [did] not prohibit the development, production, and stockpiling of 'defensive' biological weapons." Leitenberg continued "the Biological Weapons Convention does not distinguish between 'offensive' biological weapons, and any other kind. There is no such thing as 'defensive' biological weapons."[153] Leitenberg stated that the "[D]HS's choice of language in its FY2006 budget request was not an accident, but a deliberate, considered decision." He highlighted inclusion of similar language in previous draft and final Environmental Impact Statements for the NBACC facility.[154]

In apparent attempts to address these concerns in August 2005, the US Department of Homeland Security developed a formal internal management directive regarding "[C]ompliance With, and Implementation of, Arms Control Agreements" which was applicable to "all organizational entities within the Department of Homeland Security…and…US Government National Laboratories, universities, and private contractors directly engaged in work to support the Department at the federal level."[155] It required that that "[A]ll relevant research, development, and acquisition projects shall be assessed for arms control compliance at inception, prior to funding approval, whenever there is significant project change, and whenever in the course of project execution an issue potentially raises a compliance concern."[156] The DHS subsequently established both a compliance assurance programme office and a Compliance Review Group to determine whether the NBACC research activities are in compliance with the BTWC.[157]

The US Congressional Research Service reviewing the activities of the NBACC noted that:

[153] Leitenberg, M. (2005) op. cit. pp. 79–80.

[154] The new DHS BTWC treaty interpretation first appeared in the 17 September 2004, *DHS submission for comments on the Draft Environmental Impact Statement (EIS) for NBACC*, and was repeated in the final EIS released by DHS on 23 December 2004, see Leitenberg M. (2005) op. cit. p. 80.

[155] US Department of Homeland Security (2005) *Compliance With, and Implementation Of, Arms Control Agreements*. DHS Directives System MD Number: 041-01 Revision Number: 00 Approval Date: 08/26/2005 Issue Date:05/25/2007 Available at http://www.dhs.gov/xlibrary/assets/foia/mgmt-directive-041-01-compliance-with-and-implementation-of-arms-control-agreements.pdf.

[156] US Department of Homeland Security (2005) op. cit.

[157] An overview of the compliance review process was presented at the BTWC Meeting of Experts (2005) Geneva June. Available at http://daccessdds.un.org/doc/UNDOC/GEN/G05/619/03/PDF/G0561903.pdf?OpenElement.

> While such an internal compliance review process may be robust, some arms control experts have been critical of compliance processes that remain entirely internal to a single agency. Such critics assert that interagency review, or review performed or coordinated through the White House, for example through the National Security Council or the Homeland Security Council, would provide greater expert input and further divorce the compliance review from the programmatic and budgetary aspects of a research program.[158]

Since its establishment, publicly available information concerning the activities undertaken at the NBACC, and specifically the NBTCC, have been tightly controlled and certain research activities and results classified for security purposes. The relative proportion of activities openly reported and classified is uncertain and appears to have changed with NBACC leadership. According to the 2007 CRS report, originally the entire NBACC was expected to be designated as a Sensitive Compartmented Information Facility (SCIF) where classified information and materials could be stored and discussed.[159] However in a 2008 interview,[160] then incoming NBACC director, Patrick Fitch, stated that he intended to operate the NBACC with the greatest possible transparency. "[E]ighty percent of our projects and their results will be unclassified, and we will encourage our scientists to publish," He confirmed that the NBACC would be "[S]CIFable" in an emergency, though he stated that he intended to encourage as much interaction as possible between NBACC scientists and their US and foreign counterparts, stating that "[I]n such a fast-moving area it's self-defeating to isolate yourself."

The NBTCC does allow a limited range of research activities to be published in open-source papers which are detailed on its website and/or reported in the US annual BTWC CBM declarations. Whilst certain of these papers raise specific potential concerns (as detailed in Sect. 8.4), the larger concern is whether these published papers are truly indicative of the research activities being undertaken by the NBTCC. And more broadly still, whether the NBTCC and the wider US biodefence community have been or are engaged in research projects and related activities that breach the BTWC and/or the CWC and that are classified and never published in open sources.

[158] Shea, D. (2007) *The National Biodefense Analysis and Countermeasures Center: Issues for Congress.* Congressional Research Service. http://www.fas.org/sgp/crs/homesec/RL32891.pdf, p. 8.

[159] Shea, D. (2007) op. cit. p. 6.

[160] Miller, J. (2008) Bioterrorism's Deadly Math, *City Journal*, Autumn. Available at https://www.city-journal.org/html/bioterrorism%E2%80%99s-deadly-math-13123.html.

8.5.4 DARPA PREPARE Programme

In May 2018 DARPA detailed its new Pre-emptive Expression of Protective Alleles and Response Elements (PREPARE) programme which is intended to "explore ways to better protect against biological, chemical, or radiological threats by temporarily and reversibly tuning gene expression to bolster the body's defenses against—or directly neutralize—a given threat."[161]

According to DARPA:

> PREPARE diverges sharply from recent gene-editing research, which has centered on permanently modifying the genome by cutting DNA and inserting new genes or changing the underlying sequence to change the genetic code…. The envisioned PREPARE technologies would provide an alternative that preserves the genetic code exactly as it is and only temporarily modulates gene activity via the epigenome and transcriptome, which are the cellular messages that carry out DNA's genetic instructions inside cells. This would establish the capability to deliver programmable, but transient, gene modulators to confer protection within brief windows of time for meaningful intervention.[162]

Thus PREPARE will seek to "identify the specific gene targets that can confer protection, develop in vivo technologies for programmable modulation of those gene targets, and formulate cell- or tissue-specific delivery mechanisms to direct programmable gene modulators to the appropriate places in the body."[163]

The programme will initially focus on "four key health challenges"—influenza viral infection, opioid overdose, organophosphate poisoning, and exposure to gamma radiation—as "proofs of concept" for what DARPA ultimately envisions as a generalisable platform that can be rapidly adapted to emerging public health and national security threats. "[T]he ultimate objective of PREPARE is to develop a modular, threat-agnostic platform solution with common components and manufacturing architecture that can be readily adapted to diverse and emerging threats."[164]

[161] US DARPA (2018) *Dialling Up the Body's Defenses Against Public Health and National Security Threats*. 25 May. https://www.darpa.mil/news-events/2018-05-25.
[162] US DARPA (2018) op. cit.
[163] US DARPA (2018) op. cit.
[164] US DARPA (2018) op. cit.

According to DARPA, research will be conducted primarily using computer, cell culture, organoid, and animal models to establish proof of concept. However, DARPA's vision is to generate new medical countermeasures for future use in humans and consequently, DARPA is working with independent bioethicists to identify and address potential ethical, legal, and societal issues.[165]

Lentos and Littlewood noted that whilst the PREPARE programme "strives to gain knowledge and develop technological capabilities that would protect warfighters, first responders, and civilian populations and lead to greater public-health preparedness for major incidents" it would also "inevitably, entail greater awareness of populations' vulnerabilities and provide greater understanding of how to deliver programmable gene modulators to reduce protections (that is, to lower the human body's natural defense)".[166] Such research projects and the dual-use issues they raise may not at first seem to be of immediate concern but rather to be future potential threats. However, they have to be seen in the context of the very rapid changes in our ability to access, assess and affect the brain,[167] and our understanding of key issues such as the mechanisms underlying resilience to social stress.[168]

8.6 Contemporary US Dual-Use Toxin and Bioregulator Research

For many years, US military–associated scientists have worked on countermeasures to toxin agents that could be employed against the US,[169] and much of that work necessarily has potential dual-use implications. It seems unlikely that the dual-use implications of such work would not sometimes

[165] US DARPA (2018) op. cit.

[166] Lentzos,F. and Littlewood, J. (2018) DARPA's Prepare program: Preparing for what? *Bulletin of Atomic Scientists*, 26 July. Available at https://thebulletin.org/2018/07/darpas-prepare-program-preparing-for-what/.

[167] Giordano, J. (2016) The neuroweapons threat. *Bulletin of the Atomic Scientists*, 31 May, 1–4.

[168] Isingrini, E. et al. (2016) Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. *Nature Neuroscience*, **19**(4), 560–563; Zhang, H. et al. (2019) A Key Noradrenergic Brainstem-Mesolimbic Circuit: Resilience to Social Stress. *Chronic Stress*, **3**, 1–3.

[169] Lebeda, K. J. et al. (2018) Yesterday and Today: The Impact of Research Conducted at Camp Detrick on Botulinum Toxin. *Military Medicine*, **183**(5/6), 85–95.

raise concern amongst other States. The scale and range of US activities in this area is extensive with much, but by no means all, of the relevant projects and programmes publicly reported, in for example, peer reviewed papers, the US BTWC CBM Declarations or on the relevant US facility or defence organisation websites. The following examples below drawn from publicly available sources are intended to provide an indication of some dual-use activities of potential concern.

One area of potential dual-use concern has been US biodefence research into the toxicity of aerosolised toxins. A 2003 paper described how researchers from the Division of Toxicology and Aerobiology, at the US Army Medical Research Institute of Infectious Diseases, at Fort Detrick, undertook experiments with aerosolised ricin toxin upon mice models to determine the impact of inhalation chamber type and aerosol particle size on the respiratory deposition and retention of ricin aerosols in the models.[170] They found a "differential lethality that is contingent upon aerosol size". In their discussion they highlighted the "paucity of data on basic deposition and retention estimates for biological threat agents in animal models commonly used in biodefense research". They stated that their "investigation provide[d] basic data for the proper development of animal models of disease that allow further understanding of the pathogenesis of highly toxic or infectious aerosols." They highlighted their intention to design "[F]uture studies… to integrate deposition estimates that assess the differential pathogenesis of heterodisperse aerosols of biological origin."[171]

A 2010 paper described a study designed to estimate inhaled 50% lethal doses (LD_{50}) and to estimate 50% lethal exposure concentrations relative to time (LCt_{50}) in rhesus macaques exposed to botulinum neurotoxin (BoNT) complex serotype A, subtype A1 (BoNT/A1), and BoNT serotype B, subtype B1 (BoNT/B1).[172] During the course of the study, a head-only aerosol exposure system was utilised to deliver target BoNT aerosol doses to the macaques. Clinical observations, body weights, clinical haematology results, clinical chemistry results, circulating neurotoxin levels, and telemetric parameters were documented to "aid in the

[170] Roy, C. et al. (2003) Impact of Inhalation Exposure Modality and Particle Size on the Respiratory Deposition of Ricin in BALB/c Mice. *Inhalation Toxicology*, **15**(6), 619–638.

[171] Roy, C., et al. (2003) op. cit. p. 636.

[172] Sanford, D. et al. (2010) Inhalational botulism in rhesus macaques exposed to botulinum neurotoxin complex serotypes A1 and B1. *Clinical and Vaccine Immunology*, **17**(9), 1293–1304.

understanding of disease progression".[173] The study was undertaken by researchers from Battelle Biomedical Research Center and DynPort Vaccine Company LLC as part of work to establish a reliable rhesus macaque aerosol challenge model for evaluating efficacy of a recombinant botulinum vaccine (rBV A/B) then being developed for protection against inhalational intoxication in humans. The study was funded by the Chemical Biological Medical Systems Joint Vaccine Acquisition Program (CBMS-JVAP), Department of Defense (DoD).[174]

Subsequently, a 2021 paper described NBTCC researchers' investigations into the toxicity of botulinum neurotoxin (BoNT) aerosols with differing particle size from 1.1 to 7.6 micron diameters, delivered via inhalation exposure to mice models. As with the 2003 Fort Detrick ricin research, the NBTCC study found that the "lethality of aerosolized BoNT is inversely related to aerodynamic particle size, with larger particle sizes requiring greater amounts of toxin to produce similar proportional lethality in mice." The researchers further noted that "[A] limited assessment of the shift in the LD_{50} as a function of aerosol particle size on toxicity of inhaled BoNT in a large animal model, such as nonhuman primates, would provide additional data to inform selection of appropriate values for use in human risk assessment, and biodefense preparedness planning."[175]

While all three studies were undertaken with the stated purpose of informing and facilitating medical countermeasure development and preparedness modelling, their findings as well as the research methodologies developed, and lines of investigation they opened up could potentially be malignly employed in the development of more effective botulinum, ricin, or other aerosolised toxin weapons.

Similar considerations could apply, for example, to advanced engineering of botulinum toxins. These toxins have different domains that eventually allow the toxic part to enter affected neurons (see Chap. 2), but the part that enters the cell can be rendered non-toxic and then used for benign purposes i.e. to carry a therapeutic cargo into neurons. US military medical researchers have been involved in such work. For example, one group of researchers which included scientists from the US Army Medical Research Institute of Chemical Defense published a paper in 2017

[173] Sanford, D et al. (2010) op. cit. pp. 1293–.

[174] Sanford, D et al. (2010) op. cit. pp. 1293 and 1304.

[175] Boydston, J. et al. (2021) Influence of aerodynamic particle size on botulinum neurotoxin potency in mice. *Inhalation Toxicology*, **33**(1), 2021, 1–7.

describing their development of a non-toxic derivative of botulinum toxin by "rationally designed amino acid substitutions" and their evaluation of its functions.[176] Similarly, another researcher based at the US Army Medical Research Institute for Infectious Diseases, Fort Detrick, published a review in 2018 detailing how botulinum toxins "have been engineered in an effort to produce new classes of therapeutic molecules to address a wide array of disorders."[177] There has long been dual-use concerns about the possible misuse of chimeric toxins produced from elements from different toxins. The ability to actually modify the final operational element that affects the function of the affected cells would appear likely to add to such concerns.

Similar considerations would apply to investigations on how these toxins move across intestinal and bronchial barriers to cause infections as the naturally produced toxin is enclosed by associated proteins that not only protect it from the environment but also facilitate its initial entry into the body. One group including a researcher from the US Army Medical Research Institute of Infectious Diseases, Fort Detrick, published a 2018 paper describing their study of the movement of botulinum toxin across human bronchial and intestinal epithelial cells using "a sensitive near infrared florescence transcytosis assay" and "microscopically using fluorescently labelled toxin and confocal microscopy."[178] Better understanding of the mechanism by which, for example, the toxin enters the body through the lungs would likely raise dual-use concerns, especially as botulism in humans is typically associated with ingestion of the causative microorganism and not through aerial delivery.

Detailed knowledge on how staphylococcal superantigens function has been reviewed by a researcher from the US Army Medical Research Institute of Infectious Diseases, Fort Detrick, the 2019 paper focused "on the signalling pathways induced by superantigens that lead to the activation of inflammation and damage response genes" in the target cells which

[176] Vazquez-Cintron, E. J. et al. (2017) Engineering Botulinum Neurotoxin C1 as a Molecular Vehicle for Intra-Neuronal Drug Delivery. *Nature Scientific Reports*, **7**: 42923. DOI: 10.1038/srep42923.

[177] Webb, R. P. (2018) Engineering of Botulinum Neurotoxins for Biomedical Applications. *Toxins*, **10**, 231; doi:10.3390/toxins10060231.

[178] Ghosal, K. J. et al. (2018) Role of critical elements in botulinum neurotoxin complex in toxin routing across intestinal and bronchial barriers. *PLOS ONE*, **13**(7). https://doi.org/10.1371/journal.pone/0199524.

result in the subsequent deleterious effects caused by the superantigen.[179] Given the increasing understanding of the likely role, for example, of autoimmune processes in narcolepsy (see Chap. 2), more and more detailed knowledge of such signalling pathways could raise dual-use concerns.

A 2017 report published by the US Army Edgewood Chemical Biological Center detailed how an ECBC-led team in 2010–2011 employed recombinant technology to produce three small batches of the non-toxic staphylococcal enterotoxin B triple mutant (L45R, Y89A, and Y94A).[180] The batches of the surrogate SEB were then tested by the US Defense Biological Products Assurance Office to "identify purity, homogeneity, and activity". Test results revealed that this product demonstrated "high levels of reproducibility and consistency in yield, purity, homogeneity, and antigenicity." The stated benign purpose of this pilot project was to assess whether recombinant technology could be employed to produce non-toxic toxin surrogates that retain the relative epitopes that would allow them to be employed in antibody-based detection platforms. However, since the 1980s there has been concern that recombinant technologies would provide advantageous means of production of toxins, so the demonstration of such technologies even at pilot scale could raise some dual-use concerns.

8.7 Measures to Facilitate Transparency: CWC Article X Declarations, BTWC CBMs, and Unilateral US Compliance Reports

Under both the BTWC and the CWC, States Parties are permitted to conduct research and associated activities including the production of appropriate quantities of potential weapons agents for "prophylactic, protection and other purposes" under the BTWC, and for "protective purposes" under the CWC. Recognising the danger that such activities could mask weapons programmes, both the OPCW and the BTWC States Parties have introduced relevant reporting and transparency mechanisms.

[179] Krakauer, T. (2019) Staphylococcal Superantigens: Pyrogenic Toxins Induce Toxic Shock. *Toxins*, **11**, 178; doi:10.3390/toxins11030178.

[180] Calm, A. et al. (2017) *Pilot scale production and testing of a recombinant staphylococcal enterotoxin SEB triple mutant, ECBC-TR1471*. Army Edgewood Chemical Biological Center Aberdeen Proving Ground, United States. Available at http://www.dtic.mil/dtic/tr/fulltext/u2/1039416.pdf.

Consequently, CWC States Parties are required under Article X of the Convention to provide annual declarations to the OPCW Technical Secretariat on "national programmes related to protective purposes". There is currently no requirement to make Article X declarations public, and the US has not done so.[181] Consequently, it is not possible for civil society to directly establish whether the US has fully reported to the OPCW on toxin and bioregulator research activities undertaken for "protective purposes".

This contrasts with the information publicly available through BTWC associated measures. Since 1989 the US has submitted confidence building measures (CBMs) to the BTWC States Parties/ISU on an annual basis, with the latest CBM submitted in 2022.[182] The US has made a version of its CBM returns publicly accessible via the BWC ISU website since 2010 and is one of just a minority of States to do so, with for example only 32 States Parties making their CBM returns publicly available in 2021.[183] With the exception of Form F on past activities in offensive and/or defensive biological research and development programmes (for which it has stated "Nothing new to declare" since 1997), the US has made extensive annual declarations in relation to each of the CBMs. Indeed, the detail and scale of its reporting appear to go beyond that provided by any other State, with US annual CBM declarations commonly exceeding 170 pages and with some surpassing this, notably the 2012 US CBM declaration which amounted to 272 pages. It should be further recognised that a number of the papers of potential dual-use concern highlighted in this case study have been listed in the US CBM Declarations. Despite these important US reporting and transparency measures, legitimate questions remain as to whether the US incorporates all relevant biodefence activities of potential concern in its CBMs, and for those activities it does include, whether it provides sufficient information for other BTWC States Parties (or civil society) to determine its intent. Particular concerns arise with regard to specific projects, research units, or entire facilities that may, in part of in full, be classified.

[181] Chemical Weapons Convention (1993) op. cit., Article X, paragraph 4.

[182] United Nations, ODA, *Confidence Building Measures, United States of America*, https://bwc-ecbm.unog.ch/state/united-states-america (accessed 26 April 2022).

[183] United Nations, ODA, *Confidence Building Measures, Submissions made by States Parties by year*, 2021, https://bwc-ecbm.unog.ch/ (accessed 26 April 2022).

In addition to the annual reporting and transparency measures under the BTWC and the CWC, the US also unilaterally undertakes compilation and publication of a public Compliance Report addressing *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. These *Arms Control Compliance Reports*, which in recent years have been produced on an annual basis, are prepared by the Department of State in consultation with the US Departments of Defense and Energy, the Joint Chiefs of Staff, and the US intelligence community.[184] They predominately detail US analysis of other States' compliance with certain arms control and disarmament treaties including the BTWC (with similar analysis of CWC compliance detailed in a parallel CWC Compliance *Report*[185]). However, these reports additionally incorporate a brief description of US compliance with the BTWC and the CWC. In certain years, such reports have highlighted instances where other States have raised concerns about US compliance, and described the, sometimes cursory, US response to such concerns.[186] In its 2022 *Arms Control Compliance Report* with regard to the BTWC, the US reported that:

> All U.S. activities during the reporting period were consistent with the obligations set forth in the Biological Weapons Convention (BWC). The United States continues to work toward enhancing transparency of biodefense work and effective national implementation of BWC obligations using the BWC confidence-building measures and a range of voluntary measures and initiatives. Additionally, the United States has been transparent about U.S. scientific and technical engagements and laboratory support provided over time, consistent with Article X that improve the international community's capacity to detect, prepare for, and respond to disease outbreaks and other biological threats.[187]

[184] US Department of State, Reports—Bureau of Arms Control, Verification and Compliance, *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*. Available at https://www.state.gov/adherence-to-and-compliance-with-arms-control-nonproliferation-and-disarmament-agreements-and-commitments/.

[185] This report entitled *Compliance with the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction*, Condition (10) (c) Report, is produced by the US Department of State on an annual basis.

[186] See for example, United States (2021) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*, State Department, April, p. 5.

[187] United States (2022) *Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments*, State Department, April, p. 5.

Despite the transparency and confidence building measures implemented by the US, a number of States, media outlets, and civil society observers have over the years raised concerns with regard to US dual-use life science research and other activities which they claim could have been directed at development of biological and toxin weapons (and some of which have been raised in this publication). The nature and strength of such concerns have, of course, varied considerably.

In recent years Russia (sometimes together with other States) has made repeated allegations relating to the US biodefence infrastructure and also US or US-funded military research facilities in third countries—including former Soviet states surrounding Russia, notably Georgia. For example, on 7 October 2021 as part of their joint statement on measures to strengthen the BTWC, the Foreign Ministers of China and Russia stated:

> United States' and its allies' overseas military biological activities (over 200 US biological laboratories are deployed outside its national territory, which function in opaque and non-transparent manner) cause serious concerns and questions among the international community over its compliance with the BWC. The two sides share the view that such activities pose serious risks for the national security of the Russian Federation and China, and are detrimental to the security of relevant regions. The Russian Federation and China further note that the United States' and its allies' military biological activities on their national territory also cause serious compliance concerns.[188]

It should be noted that official public reports and statements containing allegations regarding US activities potentially related to biological and toxin weapons, made by Russia (and other States), are generally broad in nature and do not include substantive verifiable supporting evidence. It is not known whether such information is contained in associated classified versions of such documents provided to BTWC States or the BTWC Implementation Support Unit. The veracity of previous Russian allegations has been questioned including by certain civil society researchers.[189]

[188] China and Russia (2021) *Joint Statement by the Foreign Ministers of the People's Republic of China and the Russia Federation on Strengthening the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*, 7 October 2021. Available from Chinese Ministry of Foreign Affairs website, https://www.fmprc.gov.cn/mfa_eng/zxxx_662805/t1912953.shtml.

[189] See for example: Leitenberg, M. (2020) False allegations of biological-weapons use from Putin's Russia, *The Nonproliferation Review*, **27**(4–5), 425–442.

Considering the nature of the Russian allegations and the lack of credible publicly available information that Russia has provided to justify their claims, the Russian activities appear to be part of a disinformation campaign against the US rather than an attempt at raising legitimate concerns over potential US BW-related activities.

Russian disinformation activities have increased following its invasion, on 24 February 2022, of Ukraine. On 11 March 2022, Russia initiated a debate by the UN Security Council, of its allegations that Ukraine "has a network of at least 30 biological laboratories that host extremely dangerous biological experiments, aimed at enhancing the pathogen properties of …lethal diseases with the help of synthetic biology [and that] *this work is funded and directly supervised by …the United States*" (emphasis added).[190] The UN High Representative for Disarmament Affairs, Izimu Nakamitsu, commented on the Russian allegations by stating that the "United Nations is not aware of any biological weapons programmes."[191] The Russian allegations were forcefully refuted by the US, Ukraine, and a number of additional States during the UNSC meeting[192] and also in an emergency session of UN General Assembly.[193]

Although the US government provided a response to the current authors on 9 November 2021 addressing some issues notably regarding CNS-acting chemicals, it did not provide substantive information on the US toxin and bioregulator research highlighted in this case study.[194]

8.8 Concluding Remarks

The US initiated a biological weapons programme during World War II, which expanded significantly thereafter. This programme, including work on toxins, was closed down at the beginning of the 1970s. The US subsequently

[190] United Nations Security Council (2022) *Statement by Russian Permanent Representative Vassily Nebenzia at UNSC briefing on biological laboratories in Ukraine*. 11 March.

[191] United Nations Security Council (2022) *High Representative's briefing to the Security Council on Threats to International Peace and Security, Statement by Ms. Izumi Nakamitsu, High Representative for Disarmament Affairs*. 11 March.

[192] United Nations Security Council 8991ST Meeting (AM), *Meeting coverage (2022) United Nations Not Aware of Any Biological Weapons Programmes, Disarmament Chief Affirms as Security Council Meets to Address Related Concerns in Ukraine, SC/14827*. 11 March.

[193] United Nations, (2022) *11th Emergency Special Session of the UN General Assembly on Ukraine, convened by S/RES/2623*.

[194] Gross, L. (2021) op. cit.

continued research into a range of potential incapacitating chemical agents (or CNS-acting chemicals), including bioregulators and bioregulatory pathways, for law enforcement and military purposes on and off through to the early years of this century. However, in 2013 the US stated that it rejected the development, stockpiling, and use of incapacitating chemical agent/CNS-acting weapons. In November 2021, the US stated that it "is not developing, producing, stockpiling, or using pharmaceutical-based agents".[195]

There has been a long series of concerns raised over decades about military-funded and military-related US institutions carrying out biological weapons research for defensive purposes which have been perceived by certain States and civil society observers as potentially crossing the line into offensive weapons research. Particular concerns relate to the apparent questionable US interpretation that the BTWC allows development of biological weapons when intended for threat assessment and developing defensive counter-measures.

Open-source information indicates a range of contemporary toxin and bioregulator research, of possible dual-use application, has been carried out by US military and military-related institutions and researchers. The US has provided sufficient information or allowed public reporting and publication of scientific papers on much of this research allowing a determination of their clear medical or protective purpose. However, given the lack of full public reporting and transparency for certain facilities and programmes, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied.

Given limited transparency in this area, it is unknown whether and how frequently the US provides CWC Article X declarations to the OPCW and whether they include details of toxin and bioregulator research for protective purposes. In contrast, the US is one of only a minority of States that have made their BTWC CBM submissions to the ISU/BTWC States Parties public. The US also includes a description of its own compliance with the CWC and BTWC as part of its annual *Arms Control Compliance Reports*. Despite such reporting and transparency measures, certain States, media, and civil society observers have raised concerns regarding US life science research and associated activities. However, it should be noted that some allegations, particularly by Russia, regarding purported US biological weapons-related activities appear to be part of a disinformation campaign.

[195] Gross, L. (2021) op. cit.

It would be beneficial if the US specifically addressed concerns about its previous and contemporary biological and toxin weapons-related research and associated activities through the BTWC CBM annual reporting process and its annual CWC Article X declaration, if it has not already done so. Furthermore, to increase public confidence in this area, it would be beneficial if the US published unredacted version of such reports.

In addition, it would be beneficial if the US could clarify whether its previous declarations that it was not developing, producing, or using CNS-acting chemicals cover toxin or bioregulator-based CNS-acting chemicals, and that such moratoria will be permanent. Similarly as a State leading the current initiative to prohibit the aerosolised use of CNS-acting chemicals for law enforcement, it would be useful to clarify whether the US considers that the development, production, and use for law enforcement of aerosolised toxins and bioregulators is prohibited under the CWC, and that no CWC State Party should conduct such activities.

US companies have developed 'wide area' RCA means of delivery, a number of which are potentially capable of disseminating OC (a sensory irritant of biological origin) or its synthetic analogue, PAVA, over large areas or extended distances. The US should provide details of which, if any, military, security or police forces possess stocks of these means of delivery, provide details of the nature of such stockpiles, the circumstances under which such means of delivery would be employed, and the US application of the CWC and the BTWC in this area.

US defence and defence-funded projects have researched and explored development of malodorant weapons. Certain US companies have promoted malodorants and associated means of delivery to the law enforcement and military communities. The US should provide details of which, if any, military, security, or police forces possess stocks of malodorant weapons, provide details of the nature of such stockpiles, and the circumstances under which such malodorant weapons would be employed. The US should also clarify its understanding of the application of the CWC and the BTWC with regard to malodorant weapons.

Those States that have made public allegations about the US' previous and contemporary biological and toxin weapons research and associated activities should employ the relevant consultation, and/or investigation, and fact-finding mechanisms under the CWC and BTWC as appropriate to raise and resolve their concerns.

CHAPTER 9

Regulation of Toxins and Bioregulators Under International Arms Control and Disarmament Instruments

9.1 Introduction

The norm against the deliberate use of both poison and disease as weapons of warfare can be traced back to antiquity. These ancient interconnected taboos subsequently became embodied and codified in the twentieth century and continue to this day through three international instruments: the Geneva Protocol, the Biological and Toxin Weapons Convention (BTWC), and the Chemical Weapons Convention (CWC). Collectively they establish two distinct yet overlapping regimes prohibiting chemical and biological weapons.

The Geneva Protocol, which was negotiated in 1925 as a reaction to the misuse of modern chemistry in the form of chemical gas weapons during World War I and subsequent fears about potential bacteriological warfare, prohibits the use of both chemical and biological weapons, but only in war. Recognising the limited scope of the Geneva Protocol prohibitions, the international community subsequently sought to create further international instruments to more extensively regulate chemicals and biological agents and prevent their weaponisation, as well as their use in armed conflict and more broadly for hostile purposes. To advance

The original version of this chapter was revised with Fig. 9.1 updated. The correction to this chapter can be found at https://doi.org/10.1007/978-3-031-10164-9_11

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_9

progress, during the late 1960s it was decided to separate the biological and chemical weapons treaty negotiations. This, consequently, led to the relatively quick and successful agreement in 1972 of the BTWC banning development, production, acquisition, and stockpiling of biological and toxin weapons. It subsequently took over two further decades for the international community to adopt the CWC in 1993, which in addition to prohibiting development, production, acquisition, stockpiling and use of chemical weapons also established extensive verification measures overseen by an international organisation.

The comprehensive regulatory coverage that should be provided by the BTWC and the CWC has become more and more important as the ongoing revolution in the chemical and life sciences has proceeded, particularly since the 1980s when the boundaries between chemistry and biology have become increasingly blurred. Such developments have broadened the range of potential warfare agents available to today's weaponeers as well as providing ever more powerful technologies for agent production, formulation of effective tactical mixtures, dissemination, and so on. This, in turn, has meant that the clear distinctions drawn between chemical and biological weapons have become less useful. In 2008, Julian Perry Robinson warned that:

> advances in the life sciences, coupled with technologies that allow the analysis and construction of complex biologically active molecules, would eventually make it possible to design a chemical that would interfere with *any* life process that could be understood in molecular terms. And thoughts could also turn to the idea of modifying the genes of factory or vector organisms so as to obtain such chemicals as gene products. Because of this convergence of chemistry and biology, we may eventually be able to manipulate at will the processes of development, inheritance, reproduction, locomotion, sensation, cognition and any other process that keeps us working as normal human beings. Some of the weapons providing such power could carry the identities of both CW (toxic) and BW (infective) (Original emphasis).[1]

Consequently, rather than thinking of chemical and biological weapons threats as separate, the current authors have been among those arguing that it is more useful to conceptualise such agents as lying along a continuous 'biochemical threat spectrum' running from the traditional chemical warfare agents (including nerve, blood, blister and choking agents) on one extreme, through mid-spectrum agents (including industrial chemicals, riot control agents (RCAs), malodorants, toxins, and bioregulators),

[1] Perry Robinson, J. (2008) Bringing the CBW Conventions Closer Together. *The CBW Conventions Bulletin*, **80**, p. 2.

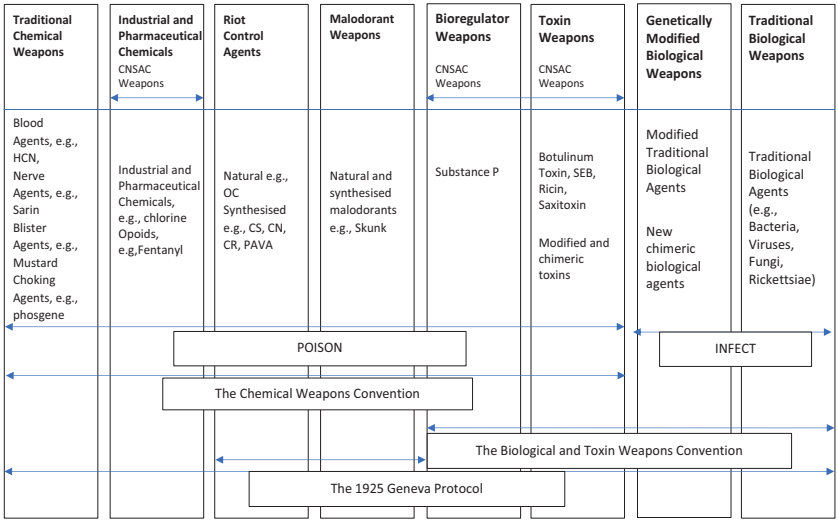

Fig. 9.1 International instruments addressing biochemical threat spectrum agents

and on to biological warfare agents (including traditional and genetically modified warfare agents).[2]

As can be seen from Fig. 9.1, certain of the mid-spectrum agents—notably toxins and bioregulators—are covered under the scope of both the BTWC and the CWC.[3] Consequently, they should be effectively regulated by both regimes. This chapter will explore whether this ideal is borne out in reality. It will briefly highlight how toxins and bioregulators are addressed under the narrowly focussed Geneva Protocol and then more extensively investigate their regulation under the more comprehensive

[2] See for example: Pearson, G. (2002) *Relevant Scientific and Technological Developments for the First CWC Review Conference: The BTWC Review Conference Experience*. CWC Review Conference Paper No. 1. University of Bradford, August; Aas, P. (2003) The Threat of Mid-Spectrum Chemical Warfare Agents. *Prehospital and Disaster Medicine*, **18**(4), 306–312.

[3] Figure 9.1 incorporates three heterodox agent categories—riot control agents, malodorants and CNS-acting chemicals—which all include certain toxins and bioregulators as well as toxic chemicals not derived from natural organisms. Consequently, whilst all agents in these three categories would be covered by the CWC, only toxins and bioregulators are additionally covered by the BTWC.

BTWC and CWC. It will explore the strengths, weaknesses, and ambiguities in these instruments and the associated measures developed by States Parties to reinforce and implement them; examining the consequent real-world consequences for regulating dual-use toxin and bioregulator research and associated activities of potential concern, and more broadly, preventing the development and use of toxin and bioregulator weapons.

9.2 Geneva Protocol

9.2.1 Overview

Under the Geneva Protocol, the States Parties acknowledged that "the use in war of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices, has been justly condemned by the general opinion of the civilised world", and declared that "this prohibition shall be universally accepted as a part of International Law, binding alike the conscience and the practice of nations."[4] They further agreed to "extend this prohibition to the use of bacteriological methods of warfare."[5]

9.2.2 Toxins, Bioregulators, and Scope of Coverage

The scope of the biological and chemical agents covered by the Protocol is considered by the majority of States to be very broad, comprising:

> (a) Any chemical agents of warfare—chemical substances, whether gaseous, liquid or solid—which might be employed, because of their direct toxic effects on man, animals or plants.
>
> (b) Any biological agents of warfare—living organisms, whatever their nature, or infective material derived from them—which are intended to cause disease or death … and which depend for their effects on their ability to multiply in the person, animal or plant attacked.[6]

[4] *Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare* (Geneva Protocol), 17th June 1925. The Protocol text and details of States Parties is available from ICRC, Treaties and States Parties to such treaties, https://ihl-databases.icrc.org/applic/ihl/ihl.nsf/Treaty.xsp?action=openDocument&documentId=921B4414B13E58B8C12563CD002D693B (accessed 25 February 2022).

[5] Geneva Protocol (1925) op. cit.

[6] United Nations General Assembly (UNGA) (1969) *Resolution 2603 A (XXIV)*, 16th December.

It is notable that whilst paragraph (b) would not appear to cover toxins or bioregulators, they would be covered under paragraph (a). However, the Protocol's prohibitions relate solely to the *use* of such agents as a weapon of war; the Protocol does not address the development, production, transfer, or stockpiling of such agents. Furthermore, the Protocol's prohibition on use is limited to situations of war. However, this prohibition, which has now become established under customary international law (and is consequently applicable to all States even if they are not party to the Protocol), is judged to apply to both international and non-international armed conflict.[7]

Although the Geneva Protocol has widespread support, its prohibitions were somewhat weakened by reservations submitted by a number of countries when becoming Parties to the Protocol, declaring that they only regarded the non-use obligations as applying to other States Parties, and that these obligations would cease to apply if the prohibited weapons were used against them. Whilst some States Parties subsequently removed such qualifications, a number still maintain their reservations on this issue. Consequently, the Protocol has been considered by certain commentators to be reduced to a *de facto* no-first-use agreement amongst States Parties. Furthermore, whilst the vast majority of States consider the use of RCAs in war completely prohibited under the Protocol, some countries do not. For example, the US upon adopting the Protocol entered a reservation, enunciated and maintained under Executive Order 11850, allowing RCA use in a range of "defensive military modes to save lives"[8] (for further discussion see Chap. 8).

9.2.3 Measures to Investigate Breaches of the Geneva Protocol

The Protocol's potential for impacting directly upon the regulation of weapons employing chemical and biological agents (including toxins and bioregulators) is constrained due to its lack of formal reporting, and direct verification and compliance measures, as well as the absence of an organisation to facilitate and monitor implementation. The international

[7] Henckaerts, J. and Doswald-Beck, L. (2005) *Customary International Humanitarian Law, Volume I: Rules*. Cambridge University Press, Cambridge. pp. 251–255, 256–259 & 259–265.

[8] Ford,G. (1975) *Executive Order 11850—Renunciation of Certain Uses in War of Chemical Herbicides and Riot Control Agents*, 8th April. 40 FR 16187 CGR, 1971–1975 Comp., 980.

community has, however, been able to utilise certain UN investigatory processes. Initially such investigations were seen as *ad hoc* one-off enquiries established under specific UN resolutions, the first being in 1980 to investigate alleged chemical weapons use.[9] The scope of such investigations was subsequently expanded in 1982 to encompass potential violations of the Geneva Protocol.[10] Building upon such experience, a 1987 UN General Assembly Resolution established a UN Secretary-General's Mechanism (UNSGM).[11] The Resolution, which included UNSGM guidelines and procedures, transformed the approach from *ad hoc* to a standing investigative mechanism and thereby formalised the methodologies that had been developed in the previous investigations. The Resolution enabled the Secretary-General to:

> carry out investigations in response to reports that may be brought to his attention by any Member State concerning the *possible use of chemical and bacteriological (biological) or toxin weapons that may constitute a violation of the Geneva Protocol or other relevant rules of customary international law* in order to ascertain the facts of the matter and to report promptly the results of any such investigations to all Member States.[12] (Emphases added)

The scope of UNSGM applicability is framed in terms of possible violation of the "Geneva Protocol or other relevant rules of customary international law" and so would clearly cover use of biological and chemical (including toxin or bioregulator) weapons in all forms of armed conflict. The authors argue that consideration should be given to exploring its application for investigating use of such weapons to commit serious human rights abuses in the absence of armed conflict. Whilst the UNSGM could be employed to investigate the *use* of toxin and bioregulator weapons, it could not be utilised to study the development, stockpiling, deployment, or transfer of such weapons where no use had taken place. However, there may, arguably, be some room for the UNSGM to investigate such activities where they bear directly upon questions of use that had taken place.

[9] United Nations General Assembly (UNGA) (1980) *Resolution 35/144* C, 12 December.
[10] United Nations General Assembly (UNGA (1982) *Resolution 37/98 D*, 13 December.
[11] United Nations General Assembly (UNGA) (1987) *Resolution 42/37 C*, 30 November.
[12] United Nations General Assembly (UNGA) (1987) op. cit. paragraph 4.

UNSGM investigations are to be conducted in accordance with the guidelines and procedures[13] endorsed by the UN General Assembly in 1990, the technical appendices of which were updated in 2007.[14] In order to conduct these investigations, lists of qualified experts, expert consultants, and laboratories are compiled and maintained. The experts and laboratories are nominated by Member States so that their services may be available for an investigation at very short notice.[15] The UN Office for Disarmament Affairs (UNODA) serves as the custodian of the Secretary-General's Mechanism. As described further in the chapter, because the BTWC (unlike the CWC) lacks an investigating body for alleged use,[16] it is particularly important to ensure that the UNSGM is effectively operational in the biological area and, accordingly, this has been the recent focus of UNODA's work in this regard.[17]

9.3 Chemical Weapons Convention

9.3.1 General Obligations Under the Chemical Weapons Convention

Article 1 of the Chemical Weapons Convention (CWC) prohibits the development, production, stockpiling, transfer and use of chemical weapons "under any circumstances".[18] States Parties are also prohibited from

[13] UN General Assembly (1989) *Chemical and Bacteriological (Biological) Weapons.* Report of the Secretary-General A/44/561, 4 October. See in particular Annex 1.

[14] United Nations Office of Disarmament Affairs (2007) *Appendices to the Secretary General's Mechanism*. Available at https://www.un.org/disarmament/wmd/secretary-general-mechanism-old/appendices/.

[15] United Nations (2019) *Fact sheet: The Secretary-General's mechanism for investigation of alleged use of chemical and biological weapons.* UNODA, July. Available at https://www.un.org/disarmament/wp-content/uploads/2019/07/SGM-Fact-Sheet-July2019.pdf.

[16] There is no other mechanism dedicated/mandated specifically to investigate the use of biological and toxin weapons. The World Health Organization (WHO) has repeatedly maintained that they have a mandate to deal with biological events even if biological and toxin weapons have been used. However, whilst the WHO mandate would include an investigative role, their focus would be completely different, that is, determining the cause and nature of the biological event in order to facilitate an effective medical response rather than for international peace and security considerations. Hence States could not simply rely on the WHO to conduct a biological and toxin weapon-use investigation.

[17] UNODA (2019) *UNSGM Fact sheet.* op. cit.

[18] Organisation for the Prohibition of Chemical Weapons (OPCW) (1993) *Chemical Weapons Convention* (CWC), Article I.

engaging in "any military preparations to use chemical weapons"[19] or to "assist, encourage or induce, in any way, anyone to engage in any activity prohibited to a State Party under this Convention."[20] In addition, Article I also requires that all existing stocks of chemical weapons[21] and chemical weapons production facilities[22] be destroyed. Although the Convention prohibits chemical weapons, it allows for the controlled peaceful use of toxic chemicals.[23]

9.3.2 Toxins, Bioregulators, and Scope of CWC Coverage

The comprehensive nature of the CWC in terms of substances covered is established under Article II(2) which defines 'toxic chemicals' as: "any chemical which through its chemical action on life processes, can cause death, temporary incapacitation or permanent harm to humans or animals.[24] *This includes all such chemicals, regardless of their origin or of their method of production*, and regardless of whether they are produced in facilities, in munitions or elsewhere"[25] (emphasis added). Given the highlighted clause, it is clear that the Convention is not restricted to chemicals manufactured by humans but would also cover those produced naturally, including certain poisons produced by living organisms, that is, toxins.

The importance of the Convention's comprehensive coverage has been widely recognised, not least by the World Health Organization in its 2004 report on the public health response to biological and chemical weapons.[26] The WHO report highlighted the dangers of the weaponisation of a spectrum of chemical and toxin agents: "now that large-scale production processes for *biologically active peptides* and similar substances are undergoing rapid commercial development, *bioregulators and other toxins* constitute a field rich in potential weapons as well as pharmaceuticals, and in

[19] OPCW, CWC, (1993) op. cit. Article I.1.c.
[20] OPCW, CWC, (1993) op. cit. Article I.1.d.
[21] OPCW, CWC, (1993) op. cit. Article I.3.
[22] OPCW, CWC, (1993) op. cit. Article I.4.
[23] OPCW, CWC, (1993) op. cit. Articles II(9) (a), V(14), and XI(2) (c).
[24] The CWC's definition of "toxic chemical" does not include toxicity against plants. Instead, the CWC makes reference to herbicides only in the *Preamble*, where it recognises the prohibition of their use as a method of warfare.
[25] OPCW, CWC, (1993) op. cit. Article II.2.
[26] World Health Organization (2004) *Public health response to biological and chemical weapons: WHO Guidance*, Second Edition. WHO, Geneva.

particular weapons of intense disabling or incapacitating power" (emphasis added).[27] It subsequently noted that "[I]t is fortunate, therefore, that this advance in biotechnology should have coincided with the adoption of the *Chemical Weapons Convention*, since it *places its States Parties under the express obligation to ensure that bioregulators and other toxins*, like all other toxic chemicals, *are used only for the purposes that the Convention does not prohibit.*" (Emphases added).[28]

9.3.3 Toxins, Bioregulators, and the Definition of Chemical Weapons

Whilst the Convention includes, in one of its annexes, three Schedules of toxic chemicals and precursors, these are specifically "identified for the application of verification measures"[29] and are not intended in any way to delineate or restrict the range of chemicals that may be considered to be "chemical weapons" under the Convention. Instead the Convention defines such weapons under Article II(1) as the following, together or separately:

> (a) toxic chemicals and their precursors, *except where intended for purposes not prohibited under this Convention, as long as the types and quantities are consistent with such purposes;* (Emphasis added)
>
> (b) munitions and devices specifically designed to cause death or other harm through the toxic properties of those toxic chemicals specified in subparagraph (a), which would be released as a result of the employment of such munitions and devices;
>
> (c) any equipment specifically designed for use directly in connection with the employment of the munitions and devices referred to in (b).[30]

A critical aspect of this definition—allowing it to be comprehensive, open-ended and flexible—is the italicised text in Article II(1)(a) which has become known as the General Purpose Criterion (GPC). Krutszch and Trapp emphasised the implications of this formulation:

[27] World Health Organization (2004) op. cit. p. 216.

[28] World Health Organization (2004) op. cit. p. 216; Chemical Weapons Convention, Article VI(1).

[29] OPCW, CWC, (1993) op. cit., Article II.(2).

[30] OPCW, CWC, (1993) op. cit., Article II.1.

> Under this concept, *all* toxic or precursor chemicals are regarded as chemical weapons *unless* they have been developed, produced, stockpiled, or used for purposes *not* prohibited. The definition thus covers any toxic or precursor chemical if intended for chemical weapons purposes, irrespective of whether it has been listed in one of the Schedules. (Original emphasis)[31]

Indeed the use of the toxic properties of *any* chemical (including natural toxins and bioregulators, as well as their synthetic analogues) as a weapon against either humans or animals—even those chemicals not originally developed or intended for such purposes—is captured by the GPC. Furthermore, because the GPC establishes a prohibition based on intent rather than on a limited list of toxic chemical agents, it allows the Convention to accommodate and reflect developments in science and technology; consequently, as Meselson and Perry Robinson have highlighted, "even toxic chemicals whose existence is not yet known are covered" by its provisions.[32]

To determine whether the use of a toxin, bioregulator or other toxic chemical would be in conformity with the CWC, the intention or purpose for its use needs to be established. The range of "purposes not prohibited" under the CWC has been defined under Article II.9 as:

> (a) Industrial, agricultural, research, medical, pharmaceutical or other peaceful purposes;
> (b) Protective purposes, namely those purposes directly related to protection against toxic chemicals and to protection against chemical weapons;
> (c) Military purposes not connected with the use of chemical weapons and not dependent on the use of the toxic properties of chemicals as a method of warfare;
> (d) Law enforcement including domestic riot control purposes.[33]

Consequently, any toxins or bioregulators (whether naturally occurring or artificially synthesised) that are developed, held, or utilised for purposes not provided for in Article II.9 are chemical weapons and prohibited under the CWC. Furthermore, the use of toxins and bioregulators for

[31] Krutzsch, W. and Trapp, R. Article II: Definitions and Criteria, in Krutzsch, W., Meyjer, E. and Trapp, R. (2014) *The Chemical Weapons Convention: A Commentary*, Oxford University Press, 2014. p. 77.

[32] Meselson, M. and Robinson, J. P. (1994) New Technologies and the Loophole, Editorial, *Chemical Weapons Convention Bulletin*, **23**, 1–2.

[33] OPCW, CWC, (1993) op. cit. Article II.9.a-d.

"purposes not prohibited" would be acceptable only "as long as the types and quantities [of these toxins and bioregulators] are consistent with such purposes."[34]

9.3.4 Measures to Facilitate Implementation, Verification, and Compliance

The CWC is implemented by its States Parties with the assistance of the Organisation for the Prohibition of Chemical Weapons (OPCW).[35] The OPCW comprises all CWC States Parties together with a Technical Secretariat with approximately 500 staff, headed by the Director General. The Technical Secretariat carries out the daily work of monitoring, verifying and facilitating implementation of the CWC.[36] It receives State Parties' declarations, detailing chemical weapons-related activities or materials and relevant industrial activities. After receiving declarations, the Technical Secretariat inspects and monitors States Parties facilities and activities that are relevant to the CWC, aiming to ensure compliance.[37]

The CWC categorises certain individual toxic chemicals and families (groups of related chemicals) and precursors into three Schedules, which are subject to routine reporting, control, and verification measures by the Technical Secretariat, to ensure they are not misused for chemical weapons purposes. Schedule 1 chemicals and precursors pose a 'high risk' to the Convention; many have been developed, produced, stockpiled, and used as chemical weapons in the past, and they have few if any peaceful uses. Schedule 2 chemicals pose a 'significant risk' to the Convention because they can be directly used as chemical weapons or used as precursors in the production of Schedule 1 chemicals or other Schedule 2 chemicals. Schedule 3 chemicals are usually produced in large quantities for 'purposes not prohibited' by the CWC but still pose a risk to the Convention because they are precursors to Schedule 1 or 2 chemicals, or have been stockpiled as chemical weapons. Although the Schedules should be reviewed and updated as required, the first, and to date only such revision took place in November 2019 with the addition of several chemicals associated with the

[34] OPCW, CWC, (1993) op. cit. Article II.1.a.
[35] OPCW, CWC (1993) op. cit. Articles VIII.1 to VIII.8
[36] OPCW, CWC (1993) op. cit. Articles VIII.37 to VIII.47
[37] OPCW, CWC (1993) op. cit. Articles VIII.37 to VIII.47

Novichok family of nerve agents and some carbamates to Schedule 1.[38] Currently two toxins—ricin and saxitoxin—are considered to be Schedule 1 chemicals.[39] Consequently, any facility that produces more than 100 grams per year of either toxin must be declared and opened to routine on-site inspection, and transfers of small quantities of either toxin must be reported. Moreover, if such Schedule I chemicals were intended for protective purposes, any amount above zero would trigger declaration and verification. Whilst noting these two important exceptions, the vast majority of toxins and all bioregulators of potential concern are not included in any of the CWC Schedules and consequently lie outside the OPCW's routine reporting, control, and verification procedures.

In addition to routine verification measures, the CWC incorporates a range of consultation, clarification, and fact-finding mechanisms that a State Party can initiate when it is concerned about the possible misuse of any toxic chemicals (including non-Scheduled chemicals) or other possible non-compliance by another State Party.[40] These mechanisms range from informal bilateral consultations to full-fledged challenge inspections and investigations of alleged use of chemical weapons. They include on-site challenge inspections of any facility or location in the territory or in any other place under the jurisdiction or control of another State Party.[41] If such procedures fail to clarify the situation or do uncover evidence of non-compliance, the matter must be passed to the Executive Council (EC) or to a Special Session of the Conference of States Parties (CSP) for resolution.[42] Despite previous and contemporary reports that certain States may have undertaken research and development of toxin weapons, no CWC State Party has initiated formal CWC multilateral consultation, clarification, and fact-finding mechanisms to resolve such matters.[43]

[38] OPCW (2019) *Decision: Changes to Schedule 1 of the Annex on Chemicals to the Chemical Weapons Convention*. C-24/DEC.5, 27 November; OPCW (2019) *Decision: Technical Change to Schedule 1(A) of the Annex on Chemicals to the Chemical Weapons Convention*. C-24/DEC.4, 27.

[39] OPCW, CWC (1993) op. cit. *Chemical Weapons Convention*: *Annex on Chemicals, B. Schedules of Chemicals, Schedule 1.*

[40] OPCW, CWC (1993) op. cit. Article IX.

[41] OPCW, CWC (1993) op. cit. Articles IX.8 to IX.25.

[42] OPCW, CWC (1993) op. cit. Articles IX.3 to IX.7, IX.23.

[43] It should be noted, however, that certain CWC States Parties have raised and sought to address toxin-related concerns through other means within the OPCW. See, for example, Chapter 7 for discussion on concerns regarding the accuracy and completeness of Syria's CW declaration, including with respect to ricin and the consequent establishment and work of the OPCW Declaration Assessment Team to attempt to resolve these issues.

9.3.5 Assessing and Responding to Science and Technology Developments

Advances in science and technology can significantly alter the implementation environment of the CWC, and they may even affect the scope of its prohibitions. Consequently the Convention makes provision for the establishment of a Scientific Advisory Board (SAB) to provide independent technical advice to the Director General and through him to the States Parties concerning developments in relevant science and technology and how they may affect operation of the Convention.[44] The SAB is normally not asked and does not express its views on matters of policy but restricts its recommendations to technical issues related to the Convention's implementation. It is noteworthy that the first substantive technical issues that the States Parties tasked the SAB to examine were toxin-related, concerning ricin production and the regulation of saxitoxin transfers, and that subsequently the Board has examined toxins in a number of its reports. In 2013, a Temporary Working Group (TWG) of the Scientific Advisory Board examined toxins and bioregulators as a part of a broader review of the convergence of biology and chemistry and its implications for the CWC.[45] Both toxins and bioregulators were subsequently examined again in the SAB's 2018 review of science and technology for the Fourth Review Conference.[46]

The 2018 SAB report emphasised that "[T]oxins are subject to the general purpose criterion under the Convention and two are in Schedule 1: saxitoxin and ricin." The SAB further noted that although not listed under any of the CWC Schedules, "[H]istorically, a third toxin—staphylococcal enterotoxin B—has also been weaponised."[47] The SAB Report summarised the characteristics of these three toxin types, highlighting their diversity of form and function. The report concentrated on the technical difficulties faced in detecting and analysing ricin and saxitoxin and how they could be mitigated, recommending that "standardised methods

[44] OPCW, CWC (1993) op. cit. Article VIII, paragraph 21(h) and 45.

[45] OPCW (1997), *Report of the Second Session of the Conference of States Parties*, C-II/8. OPCW, The Hague.

[46] Scientific Advisory Board (SAB) (2018) *Report of the Scientific Advisory Board on Developments in Science and Technology for the Fourth Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention*, RC-4/DG.1. OPCW, The Hague, 30 April.

[47] OPCW, SAB (2018) op. cit. paragraph 105

for identification and analysis of [these two toxins] should continue to be developed."[48] It further recommended that "methods for identification and analysis of other toxins that have been weaponised, or pose a high risk of use as chemical weapons, should be considered for inclusion in future biotoxin exercises."[49]

The 2013 TWG on Convergence's report appeared to consider that bioregulators were of less immediate threat to the Convention than toxins, a position essentially reaffirmed by the SAB in its Report to the Fourth CWC Review Conference, which stated that "[N]o data have been published that suggests that any individual-active peptide should be regarded as a chemical of concern."[50] And furthermore that "the potential of peptides for development as incapacitating agents may have been overstated by some commentators."[51] However, the SAB appeared less sanguine about future developments. It noted that bioregulators "can be chemically modified to increase their potency and toxicity" and that "[A]dvances in nanotechnology could potentially help transport bioregulators across the BBB [blood–brain barrier], overcome host defences, and target specific organs." And furthermore that "some peptides that cause bronchoconstriction by interaction with receptors on the surface of the lung have been reported to have moderate to high inhalation toxicity in small rodent species."[52]

In January 2021 the Director General established a SAB Temporary Working Group on the analysis of biotoxins. Its terms of reference noted that "[I]n the past, several biological toxins were weaponised…. Further, there are some biological toxins that are of interest to non-state actors. Accordingly, the capability to detect, identify, and characterize biological toxins that may be present in samples taken during investigations is essential for the OPCW."[53] Among the technical questions that the SAB TWG has been asked to consider are two of particular importance to this publication, namely: "[W]hat classes of biological toxins are most likely to be

[48] OPCW, SAB (2018) op. cit. paragraph 113
[49] OPCW, SAB (2018) op. cit. paragraph 114
[50] OPCW, SAB (2018) op. cit. paragraph 118
[51] OPCW, SAB (2018) op. cit. paragraph 119
[52] OPCW, SAB (2018) op. cit. paragraph 118
[53] Scientific Advisory Board (SAB) (2021) Terms of reference for the temporary working group on the analysis of biotoxins, Annex 2, in: *Report of the SAB at its Thirty-First Session, 3–4 March 2021*, SAB-31/1. OPCW, The Hague, 4 March 2021

relevant in investigations of alleged use?"[54] and "[A]re there other relevant compounds of biological origin that should also be considered based on their potential for misuse or technological change associated with them?"[55] The SAB TWG will have a two year lifespan and report its findings to the SAB.

9.3.6 Regulating Toxin and Bioregulator Research and Related Activities

The CWC does not explicitly prohibit research relating to chemical weapons (e.g. if it is for "protective purposes") but instead prohibits the development and production of such weapons under Article I. However, where research is an intrinsic part of a weapons development programme, it will clearly fall within the scope of the Article I prohibition. There appear to be four potential scenarios where research into toxins, bioregulators, and other biologically active peptides that could be employed as weapons may fall within the scope of the CWC, triggering different obligations upon CWC States Parties.

9.3.6.1 Scenario 1: State Research and Development of Toxin and Bioregulator Weapons Intended for Armed Conflict

The use in armed conflict of the toxic properties of chemical agents is absolutely prohibited,[56] as is their development (and by implication, associated research), production, acquisition, stockpiling, retention, or transfer when intended for such purposes, under Articles I and II. If States have undertaken programmes to research and develop toxins, bioregulators, and/or associated means of delivery for such purposes, they are required to halt such activities, declare any chemical weapons and chemical weapons production facilities (CWPFs) they possess (under Article III[57]), and ensure they are verifiably destroyed (under Article I, and in accordance with Articles IV and V respectively[58]). It should however be noted that in practice, certain facilities working with toxins and bioregulators may not currently be considered as falling under the definition of a CWPF as they

[54] OPCW, SAB (2021) op. cit. 5(b)

[55] OPCW, SAB (2021) op. cit. 5(c)

[56] In addition to the Chemical Weapons Convention, the use of toxins in armed conflict is prohibited under the 1925 Geneva Protocol and customary international humanitarian law.

[57] OPCW, CWC (1993) op. cit., Article III (1)a-c.

[58] OPCW, CWC (1993) op. cit., Article I (2) and (4); Article IV and Article V.

either would not produce a Schedule 1 chemical or would not cross the annual production capacity threshold of one tonne per year for non-Schedule 1 chemicals. Consequently, such facilities would not currently trigger corresponding declaration and destruction requirements under the CWC.[59]

9.3.6.2 Scenario 2: State Research and Development of Toxin and Bioregulator Weapons Intended for Law Enforcement Purposes

Toxin and Bioregulator RCAs

Article II.7 defines RCAs as: "[A]ny chemical not listed in a Schedule [of prohibited chemicals], which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure."[60] According to Krutzsch and Trapp's CWC Commentary, "RCAs have physiological effects corresponding to those set out in the definition of 'toxic chemicals' in paragraph 2 [Article II of the CWC]".[61] The use of RCAs as a "method of warfare" is expressly prohibited under Article I.5 of the CWC.[62] As toxic chemicals, the use of RCAs is permitted for a limited range of purposes defined under Article II.9, notably "Law enforcement including domestic riot control",[63] but only "as long as the types and quantities [of toxic chemicals] are consistent with such purposes".[64] In 2013, the OPCW Director General recognised that the CWC definition of RCAs "leaves some room for interpretation as to which chemicals can be considered as meeting the requirement specified."[65] Consequently, in 2014 the OPCW Technical Secretariat and Scientific Advisory Board developed, and in 2017 reviewed, a non-exhaustive and indicative list of 17 chemicals that corresponded to the Article

[59] OPCW, CWC (1993) op. cit., Article IV. See in particular Article IV, 8 (a) (i) and (b)(i).

[60] Krutzsch, W, and Trapp, R. Article II: Definitions and Criteria, in Krutzsch, W. Meyjer, E. and Trapp, R. (2014) op.cit. p. 88.

[61] Krutzsch, W, and Trapp, R. Article II: Definitions and Criteria, in Krutzsch, W. Meyjer, E. and Trapp, R. (2014) op.cit. p. 88.

[62] OPCW, CWC (1993) op. cit. Article I.5.

[63] OPCW, CWC (1993) op. cit. Article II(9)d.

[64] OPCW, CWC (1993) op. cit. Article II.1.a.

[65] OPCW (2013) *Report of the Twentieth Session of the Scientific Advisory Board*, SAB-20/1, 10th–14th June 2013. OPCW, the Hague, 14th June. *Annex 4, Director-General's Request to the Scientific Advisory Board to consider which riot control agents are subject to declaration under the Chemical Weapons Convention.*

II.7 definition and could therefore be considered as riot control agents and subject to declaration under the CWC.[66] Whilst this list contained no bioregulators, it did include six capsaicinoid sensory irritants of biological origin and a further chemically synthesised analogue, PAVA.[67] Given that such sensory irritants are toxic chemicals of biological origin (or synthetic analogues thereof), the authors would argue that they should all be considered to be toxin-based RCAs. Under Article III, States Parties are required to submit an initial declaration to the OPCW Technical Secretariat of all chemicals that are kept for riot control purposes, with an additional requirement that States subsequently update this declaration to reflect changes in national RCA possession.[68] The OPCW reported that, as of 31 December 2019, a total of 137 States Parties had declared possession of riot control agents, with 35 declaring possession of "capsaicinoids".[69] As part of its considerations, the SAB also established a list of 43 "substances that do not meet the criteria of an RCA but have historically been considered for use as an RCA", this included two toxins, (Z,E)-propanethial S-oxide and piperine.[70] Whilst the SAB analysis is non-exhaustive and advisory, its findings should be given due weight by all States Parties. Consequently, no substance identified by the SAB as being inappropriate for use as an RCA should be held or employed for such purposes. If research and development of additional chemicals (including toxins and bioregulators) as candidate RCAs is being conducted, care should be taken

[66] Technical Secretariat, Office of Strategy and Policy (2014), *Note by the Technical Secretariat, Declaration of riot control agents: advice from the Scientific Advisory Board*, S/1177/2014. OPCW, The Hague, 1st. See also Scientific Advisory Board (2017) *Response to the Director-General's Request to the Scientific Advisory Board to consider which riot control agents are subject to declaration under the Chemical Weapons Convention*. SAB-25/WP.1. OPCW, The Hague, 27 March.

[67] OPCW, SAB (2017) op. cit. Annex 4. The six capsaicinoids are Oleoresin capsicum (OC); 8-Methyl-N-vanillyl-trans-6-nonenamide (capsaicin);8-Methyl-N-vanillylnonamide (dihydrocapsaicin); N-Vanillyl-9-methyldec-7-(E)-enamide (homocapsaicin); N-Vanillyl-9-methyldecanamide (homodihydrocapsaicin); N-Vanillyl-7-methyloctanamide (nordihydrocapsaicin); and the synthetic analogue is N-Vanillylnonamide (pseudocapsaicin, PAVA). See OPCW, Technical Secretariat (2017) op. cit.; Timperley, C. et al. (2018) Advice from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons on riot control agents in connection to the Chemical Weapons Convention. *RCA Advances*, **8**, 41731. DOI: 10.1039/cBra08273aracli/rca-advances.

[68] OPCW, CWC (1993) op. cit. Article III).1.e.

[69] Conference of States Parties (2021) *Report of the OPCW on the implementation of the CWC in 2019*, C-25/4, Annex 4. OPCW, The Hague, 20 April 2021.

[70] See OPCW, SAB (2017) op. cit. Annex 5.

to ensure that such substances fulfil the definition under Article II.7, guided by the considerations of the SAB.[71]

Whilst the SAB has explored the types of chemicals that can be employed as RCAs, it has not been requested to investigate, nor provide guidance, as to the quantities of such agents that can be employed in accordance with Article II.7.[72] Such a study would be valuable given the long-standing concerns raised by health professionals regarding the deleterious health effects of inappropriate use of RCAs—including OC and PAVA—by law enforcement officials. A recurring medical concern has been their use in excessive quantities in the open air or in confined spaces where the targeted individuals cannot disperse. In such situations, serious injury or death can result from the toxic properties of the chemical agents or from asphyxiation.[73] Such concerns are exacerbated by the contemporary development of 'wide area' delivery mechanisms capable of disseminating significant quantities of RCA over extended distances or wide areas.[74] In 2013, the SAB "noted with concern isolated reports of the commercial availability of munitions apparently designed to deliver large amounts of riot control agents over long distances."[75] In 2018, the SAB further

[71] See OPCW, SAB (2017) op. cit paragraphs 3.1–3.4.

[72] Although the SAB has not provided guidance regarding quantitative issues in terms of the appropriate dose of RCAs to be employed, it has addressed quantitative issues with regard to overall stockholding of the now obsolete RCA, Adamsite. See OPCW, SAB (2000) *Report of the 3rd Session of the SAB*, SAB-III/1, paragraph 2.5(d). OPCW, The Hague, 27 April.

[73] World Medical Association, (WMA) (2015) *Statement: Riot Control Agents*, adopted by the 66th WMA General Assembly, Moscow, Russia, October.

[74] Crowley, M. (2013) *Drawing the Line: Regulation of 'Wide Area' Riot Control Agent Delivery Mechanisms under the Chemical Weapons Convention*. University of Bradford/Omega Research Foundation, April; Crowley, M. (2015) *Tear Gassing by Remote Control: The Development and Promotion of Remotely Operated Means of Delivering or Dispersing Riot Control Agents*. University of Bradford/Omega Research Foundation/Remote Control Project, December 2015; Crowley, M. (2018) *Development and Hostile Use of Toxic Chemical Means of Delivery and Dispersal*. Chapter 12 in: Crowley, M. et al. (eds.) *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*, Royal Society of Chemistry, August, pp. 332–380; Crowley, M. (2019) *Contemporary Development, Promotion and Use of Remote Control Riot Control Agent Delivery Mechanisms: Challenges for Effective State Regulation*. the 10th European Symposium on Non-Lethal Weapons, Royal Military Academy, Brussels, Belgium. 20–23 May.

[75] OPCW, SAB (2013) *Report of the Scientific Advisory Board on Developments in Science and Technology for the Third Review Conference of the Chemical Weapons Convention*, RC-3/DG.1, 8–19 April, Paragraph 56. OPCW, The Hague, 29 October.

warned that availability of certain 'wide area' RCA means of delivery "opens up the possibility that they could be filled intentionally with alternate types of chemicals including CWAs [chemical warfare agents] or CNS [central nervous system]-acting compounds."[76] To date, no OPCW policy-making organ has provided guidance regarding the quantities of RCA that can legitimately be employed for law enforcement purposes nor the types of RCA means of delivery suitable for such purposes, under the CWC.

Toxin and Bioregulator CNS-Acting Weapons

Ambiguities in the CWC surrounding application of Article II 1(a) and Article II.9(d) have previously led to differing interpretations by States as to whether certain toxic chemicals beyond RCAs can legitimately be employed for law enforcement purposes. Following the Russian use of CNS-acting chemicals to end the Moscow theatre siege in 2002, CWC States Parties and civil society organisations raised concerns regarding the consequences of further development, proliferation and use of weapons employing such chemicals in law enforcement. Since 2019 discussions within the OPCW focused on whether use of aerosolised CNS-acting toxic chemicals for law enforcement purposes was permissible under the CWC.

On 1 December 2021, the 26th Conference of States Parties to the CWC (CSP-26) adopted an "Understanding"—on the aerosolised use of CNS-acting chemical agents for law enforcement purposes, which "Decided that the aerosolised use of CNS-acting chemicals is understood to be inconsistent with law enforcement purposes as a "purpose not prohibited" under the Convention."[77] This CSP Decision did not introduce a new prohibition but rather clarified the correct application of the existing prohibitions and rules of the CWC. The Decision also noted that "munitions and devices specifically designed to cause death or other harm" through the release of aerosolised CNS-acting chemicals would "constitute a 'chemical weapon'",[78] and consequently should be declared and

[76] OPCW, SAB (2018) *Report of the Scientific Advisory Board on Developments in Science and Technology for the 4th Review Conference of the Chemical Weapons Convention*, RC-4/DG.1, 21–30 April, Paragraph 154. OPCW, The Hague, 30 April.

[77] Conference of States Parties (2021) *Decision: Understanding regarding the aerosolised use of central nervous system-acting-chemicals for law enforcement purposes*, C-26/DEC.10. OPCW, The Hague, 1 December.

[78] Conference of States Parties (December 2021) op. cit.

verifiably destroyed. Whilst 85 States supported the Decision, 10 States—including China, Iran, and Russia—voted against it. On 29 November 2021, China, Iran, Russia,, and Syria issued a joint statement declaring their rejection of the Decision, which they considered to be "an *ultra vires* act" that "went beyond the powers and functions of the Policy-Making Organs of the OPCW", and "so could not have any legal effect(s) on the States Parties' rights and obligations under the Convention."[79] In addition to the contested nature of its adoption and legal status, aspects of the Decision are ambiguous. Although it addresses "CNS acting chemicals", there is no definition of this phrase, nor an indication of the range of chemicals that would be covered by it. It is also limited in its scope—its prohibitions are specifically restricted to *CNS-acting* chemicals. Consequently, any existing or future law enforcement weapons that use toxic chemicals that act on other human physiological processes would not be covered by this prohibition. The Decision is further limited in the scope of the means of delivery addressed. It explicitly prohibits only *aerosolised* CNS weapons, excluding other delivery mechanisms such as the Chinese law enforcement CNS weapon highlighted in Chap. 3 of this publication. The Decision further restricts application to "munitions and devices *specifically designed* to cause death or other harm" and therefore the use of general-purpose munitions and delivery devices such as air blowers and aerosol delivery systems may not be covered. In summary, although this Decision is a significant advance in constraining weaponised use of CNS-acting chemicals, its full implications will only become apparent as States Parties further clarify outstanding areas of ambiguity in the text and attempt to implement it. Consequently, the permissibility under the CWC of research, development, and use of law enforcement weapons employing pharmaceutical chemicals, toxins, and bioregulators, is likely to remain unclear and contested.[80]

[79] Iran (2021) *Joint Statement on behalf of 4 Delegations*. Delivered by the Delegation of the Islamic Republic of Iran at the 26th Session of the Conference of States Parties of the OPCW under the Subitem 26.1 "Any Other Business" on the Draft Decision entitled "Understanding Regarding the Aerosolized Use of Central Nervous System-Acting Chemicals for Law Enforcement Purposes". OPCW, The Hague, 29 November.

[80] Crowley, M. and Dando, M. R. (2022) Central nervous system weapons dealt a blow, *Science*, **375** (6577), 153–154.

Malodorant Toxin and Bioregulator Weapons

Although there is no internationally agreed definition, the authors contend that malodorants can be considered as a disparate group of naturally occurring and synthesised chemicals affecting the human olfactory receptors, employed to elicit short-term and temporary physiological effects or behavioural responses. Defence and law enforcement bodies of certain States—including India, Israel, and the US—have undertaken research and/or explored development of a variety of malodorous substances and delivery mechanisms. In addition, commercial companies in Israel and the US have manufactured and/or promoted a limited range of malodorant weapons. Contemporary reported State use of these weapons has been limited to Israel, where Israeli military and police forces have employed malodorants for law enforcement purposes: that is for crowd control and dispersal, in a manner analogous to the use of RCAs. The candidate malodorants examined, as well as those utilised to date, typically elicit strong aversion or avoidance responses in those targeted, whilst physiological responses can include nausea, choking, gagging, and vomiting. Both the behavioural and physiological effects appear analogous to certain RCAs in terms of nature, severity, and duration. Insufficient information exists as to the long-term health effects of malodorant weapons.

From the, albeit limited, publicly available information, the authors contend that at least certain naturally occurring and synthesised malodorants fulfil the definition of toxic chemicals under Article II.2 of the CWC and as such would come under the auspices of the Convention. Furthermore, at least certain candidate malodorants also appear to fulfil the definition of riot control agents under Article II.7 of the Convention. Consequently, whilst the use of such malodorants in armed conflict would be prohibited under the CWC, they can be employed for law enforcement purposes provided the types and quantities employed were consistent with such purposes.

To date, no OPCW policy-making organ has determined whether malodorants should be considered as toxic chemicals and/or riot control agents under the CWC. It is also notable that the SAB did not address this issue in either its 2014 or 2017 analysis of substances employed as riot control agents. To date, one State Party—the US—appears to contend that at least certain malodorants (i.e. those that do not cause trigeminal nerve activation) should not be considered as RCAs under the CWC.

9.3.6.3 Scenario 3: State Research and Development of Toxins/ Bioregulators for Protective Purposes

Under Article X of the CWC, States are permitted to "conduct research into, develop, produce, acquire, transfer or use means of protection against chemical weapons, for purposes not prohibited under this Convention"[81] even where this involves production in appropriate quantities of potential chemical weapons agents, including toxins and bioregulators. The range of permissible activities established under Article X potentially allows States to mask illicit toxin or bioregulator weapons research, development, and production under the guise of "protective purposes". One area of particular potential concern, or where misconceptions can readily arise, is with regard to threat (or risk) assessment studies. As Krutzsch and Trapp have noted: "[C]hemical defence programmes sometimes include threat assessment studies related to new, hitherto unknown, agents (new lethal agents, new incapacitants). When such assessments include research work that borders on what would be undertaken in chemical weapons development, they are no longer consistent with the object and purpose of the Convention."[82]

Consequently, in order to address these concerns and to increase "transparency of national programmes related to protective purposes", Article X obliges each State Party to "provide annually to the Technical Secretariat information on its programme".[83] In 2004, the 9th Conference of States Parties (CSP) adopted a template form for States Parties to utilise when submitting their Article X.4 declarations,[84] in order to facilitate consistent implementation by a greater number of States. In its 2008 report, the SAB stated that the "potential risks" to the CWC associated with advances in science and technology would "increase significantly, should dedicated chemical weapons programmes exist and should they take advantage of new toxic chemicals."[85] Consequently, the SAB argued that

[81] OPCW, CWC (1993) op. cit., Article X, paragraph 2.

[82] Krutzsch, W, and Trapp, R (2014) Article II: Definitions and Criteria, in Krutzsch, W. Myjer, E. and Trapp, R. (eds) *The Chemical Weapons Convention: A Commentary, Oxford*, Oxford University Press. p. 93.

[83] OPCW, CWC (1993) op. cit., Article X, paragraph 4.

[84] Conference of the States Parties (2004) *Decision, Submission of information regarding national programmes related to protective purposes pursuant to Article X, Paragraph 4 of the Convention*, C-9/DEC.10. OPCW, The Hague, 30th November.

[85] Conference of the States Parties (2008) *SAB Report*, Second Review Conference RC-2/ DG.1, 28 February op. cit. paragraph 3.14.

"there is therefore good reason to call for transparency in chemical-defence programmes"[86] and recommended that the "Review Conference may wish to take this up when it addresses issues related to the annual submission by States Parties of information on their national protective programmes."[87]

Whilst publicly available OPCW reports on this issue are very limited and infrequent, as of 30 June 2019, a total of 113 States Parties had submitted information to the Technical Secretariat at some stage since 31 December 2011 on their existing national programmes for "protective purposes".[88] Although a small number of these States have unilaterally made their annual Article X declarations public, most have not. Consequently, it is not possible to determine whether the vast majority of States Parties have provided any information to the OPCW on research for "protective purposes" related to toxins or bioregulators, and if so whether such information is accurate, complete, and includes any activities of concern.

9.3.6.4 Scenario 4: Research and Development of Toxins, Bioregulators, and Delivery Mechanisms Purportedly for Medical or Other Non-prohibited Purposes, but Which Can Be Employed as Weapons

From a combined reading of Article I and Article II, development, production, acquisition, stockpiling, retention, or transfer of toxic chemicals (including toxins and bioregulators) for "[I]ndustrial, agricultural, research, medical, pharmaceutical or other peaceful purposes" would be considered as "Purposes Not Prohibited" under the CWC,[89] provided such activities conformed to the "types and quantities" restriction.[90] All States Parties are, however, required under Article VII to "adopt the necessary measures to implement [their] obligations under this Convention"

[86] Conference of the States Parties (2008) *SAB Report*, Second Review Conference RC-2/DG.1, 28 February, op. cit. paragraph 3.14.

[87] Conference of the States Parties (2008) *SAB Report*, Second Review Conference RC-2/DG.1, 28th February, op. cit. paragraph 3.7.

[88] Director General (2019) *Report by the Director General, Status of Implementation of Article X of the Chemical Weapons Convention as at 30 June 2019*. EC-92/DG.10/Corr.1. OPCW, The Hague, 4 October. Subsequent reports on Article X implementation were prepared by the Director General and reviewed by the Executive Council in 2020 and 2021, but have not been made public.

[89] OPCW, CWC (1993) op. cit. Article II(9)a.

[90] OPCW, CWC (1993) op. cit. Article II(1)a.

and shall "prohibit natural and legal persons anywhere … under [their] jurisdiction … from undertaking any activity prohibited to a State Party under this Convention, including enacting penal legislation with respect to such activity."[91]

Consequently, States Parties need to adopt and enforce the appropriate national implementation measures to ensure that no research and development activities related to toxic chemicals (including toxins, bioregulators or other biologically active peptides), ostensibly for peaceful purposes, are being utilised for activities contrary to the object and purposes of the CWC or in violation of international law, such as development of toxin weapons intended for armed conflict or human rights abuses. As well as constraining the activities of State entities, these provisions include obligations upon all States to actively prevent the development, acquisition, and use of toxin and bioregulator weapons by any non-State actors, including criminals, terrorist organisations, private military or security companies, and militias.

9.4 Biological and Toxin Weapons Convention (BTWC)

9.4.1 General Obligations Under the BTWC

The object and purpose of the BTWC is set out in the treaty's preamble:

> Determined for the sake of all mankind, to *exclude completely* the possibility of bacteriological (biological) agents *and toxins being used as weapons.* Convinced that such use would be repugnant to the conscience of mankind and that no effort should be spared to minimize this risk.[92] (Emphases added)

Article I of the BTWC establishes the principal obligations and prohibitions of the Convention, declaring that:

[91] OPCW, CWC (1993) op. cit. Article VII (1)a.

[92] ICRC, Treaties, States Parties and Commentaries: *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction* (BTWC), 1972. Available at https://ihl-databases.icrc.org/applic/ihl/ihl.nsf/INTRO/450?OpenDocument . (*Preamble*).

> Each State Party to the Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:
>
> (1) Microbial or other biological agents, or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.
> (2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.[93]

Under Article II, the BTWC requires the destruction or diversion for peaceful purposes of all agents, toxins, weapons, equipment and means of delivery specified in Article 1.[94] Under Article III the BTWC also prohibits any direct or indirect transfer of such agents, toxins, weapons, equipment and means of delivery to anyone, as well as any assistance, encouragement, or inducement of any State, group of States or international organisation to manufacture or otherwise acquire them.[95]

The BTWC does not *explicitly* establish a prohibition of the *use* of biological and toxin weapons. However, such prohibition is *implicit* through bans on the development, production, stockpiling, or acquisition or retention by other means of these agents. It would only be after one or other of these prohibitions had been breached that use could occur. Furthermore, under Article VIII, the BTWC invokes the provisions of the 1925 Geneva Protocol which explicitly contain such a prohibition.[96] The BTWC States Parties have clarified their collective interpretation that any use of a biological or toxin weapon would imply a violation of the BTWC, and this has been repeatedly affirmed by the BTWC State Parties in Extended Understandings enunciated in the Final Declarations of, for example, the Fourth,[97] Sixth,[98] and Seventh[99] and Eighth Review[100] Conferences.

[93] BTWC (1972) op. cit. Article 1.

[94] BTWC (1972) op. cit. Article II.

[95] BTWC (1972) op. cit. Article III.

[96] *Geneva Protocol for the Prohibition in War of Asphyxiating, Poisonous or other Gases, and Bacteriological Methods of Warfare*, 17 *June 1925.*

[97] United Nations (1996) *Final Document of the Fourth BTWC Review Conference*. BWC/CONF. IV/9, 25th November–6th December. Article I, paragraph 3.

[98] United Nations (2006) *Final Document of the Sixth BTWC Review Conference*. BWC/CONF.VI/6, 20th November–8th December. Article I, paragraph 3.

[99] United Nations (2011) *Final Document of the Seventh Review Conference*. BWC/CONF. VII/7, 5th–22nd December. Article I, paragraph 3.

[100] United Nations (2016) *Final Document of the Eighth Review Conference*. BWC/CONF. VIII/CRP.2, 7th–25th November. Article I, paragraph 3.

9.4.2 Toxins, Bioregulators, and the Scope of Coverage

As with the CWC, the BTWC contains a General Purpose Criterion, under Article I (1) that links the Convention's prohibitions to "types and quantities" that have "no justification for prophylactic, protective or other peaceful purposes." This allows the Convention to be 'open' in scope and thereby cover the full range of biological agents and toxins, even those that have not been discovered or synthesised yet.

Article 1 of the BTWC together with the Extended Understandings agreed at successive BTWC Review Conferences, make it clear that the Convention is intended to be fully inclusive with regard to the range of substances which it covers and also the potential targets (which include plants, as well as animals and humans). For example, the *Final Declaration* of the Eighth Review Conference of 2016 reaffirmed that:

> *all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of their origin and method of production* and whether they affect humans, animals or plants, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes, *are unequivocally covered by Article I.*... [and that] ... *Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention.*[101] (Emphases added)

Unfortunately, the term 'toxins' has not been explicitly defined under the Convention nor has a definition been collectively agreed subsequently by BTWC States Parties in their Extended Understandings. However, as discussed in Chap. 1 of this publication, certain medical bodies, notably the WHO, have sought to explore the range of substances covered by this term,[102] and certain States have explicitly defined toxins in their national measures. Consequently, toxins are commonly taken to denote chemical compounds produced by living organisms that are toxic or harmful to another living organism; and although this has not been formally recognised by the BTWC States Parties in terms of a toxin definition, there appears to be a general acceptance of such wide scope by the States Parties when addressing toxins. This interpretation appears to be reinforced by

[101] United Nations (2016) *Final Document of the Eighth Review Conference*. BWC/CONF. VIII/CRP.2, 7th–25th November. Article I, paragraphs 1 & 2.

[102] See, for example, World Health Organization (2004) *Public health response to biological and chemical weapons: WHO Guidance*, Second Edition. WHO, Geneva. Annex 2: Toxins.

application of the UN Vienna Convention on the Law of Treaties This stipulates that in the absence of a specific definition of an item in the treaty under consideration, "a treaty shall be interpreted in good faith *in accordance with the ordinary meaning to be given to the terms of the treaty in their context and in the light of its object and purpose*" (emphasis added).[103]

Similarly, the term 'other biological agents' has not been defined by BTWC States Parties, but can once again be considered extensive in the range of substances encompassed. As Chevrier and Leonard have noted: "[T]he ordinary meaning of 'other biological agents', unmodified by any restricting adjectives or clauses, implies a very broad scope, provided that broad scope is consistent with the object and purpose of the Convention."[104] Consequently, taken collectively 'toxins' and 'other biological agents' would appear to encompass a very broad range of potential agents. In this regard a number of BTWC States Parties including the Netherlands, the Russian Federation, Sweden, the UK and the US have specifically recognised the relevance of peptides, bioregulators, and their analogues to the BTWC, and highlighted the potential dangers that misuse of such chemicals could pose.[105]

For example, in its 2011 submission to the Implementation Support Unit (ISU) review of "new scientific and technological developments relevant to the Convention",[106] conducted in advance of the Seventh Review Conference, the UK included a discussion of neuroscience, in which it stated that:

> Developments in this area could also result in the identification of compounds with potential for misuse as biological *or toxin weapons agents* since

[103] United Nations (1969) Vienna Convention on the Law of Treaties, 23 May 1969, Article 31.

[104] Chevrier, M. and Leonard, J. (2007) Incapacitating Biochemicals and the Biological Weapons Convention, pp. 209–224, in: A. Pearson, et al. (Eds.) *Incapacitating Biochemical Weapons*, Lanham, MD.: Lexington Books. p. 211.

[105] See relevant *National Background Papers on Scientific and Technological Developments Relevant to the Biological Weapons Convention*, prepared for the Sixth Review Conference. Available from http://www.opbw.org.

[106] United Nations (2011) Seventh Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, *New scientific and technological developments relevant to the Convention, Background Information Document Submitted by the Implementation Support Unit.* BWC/CONF.VII/INF.3/Add.1 23 November.

> drugs acting on the brain to produce toxic or incapacitating effects could also have utility in a BW programme. *Methods to facilitate delivery of such agents could also be exploited for harmful purposes, for example, to facilitate the entry of peptide neurotoxins across the BBB [blood–brain barrier]*. However, *the prohibitions of Article I of the BTWC fully cover all such biological agents and toxins, whether naturally occurring or artificially created, regardless of their origin or method of production*.[107] (Emphases added)

Similar concerns were highlighted by the ISU in its 2011 synthesis report of scientific and technological advances prepared for the Seventh Review Conference. Considering neurobiology amongst the range of "advances with potential for weapon applications", the ISU stated that: "[S]ince the last review conference, there have been advances in: understanding the role of neuroregulators; how to influence psychological states and alter physical performance."[108] This inclusion of neuroregulators by the ISU in its analysis of "[N]ew scientific and technological developments *relevant* to the Convention" underlines the general acceptance of bioregulators as being within the BTWC scope.

In their Extended Understandings, the BTWC States Parties have clarified that the range of substances covered by the BTWC Article 1 prohibitions further extends to include all artificially created or altered microbial and other biological agents and toxins, as well as their components. This position has subsequently been reaffirmed, and its importance highlighted, by certain individual State Parties. For example, during discussions at the September 2021 BTWC Meeting of Experts (MX-2) to Review of Developments in the Field of Science and Technology Related to the Convention, the US stated:[109]

> Toxins are covered by the Chemical Weapons Convention, but they are also covered by the Biological and Toxin Weapons Convention…. So there is a

[107] United Nations (2011) *New scientific and technological developments relevant to the Convention, Addendum: Submissions from States Parties*, BWC/CONF.VII/INF.3/Add.1November. op. cit. Paragraph 125.

[108] United Nations (2011) *New scientific and technological developments relevant to the Convention, Background information document submitted by the Implementation Support Unit,* 7th BTWC Review Conference, *BWC/CONF.VII/INF.3, 10 October*. Paragraph 13.

[109] *Intervention by United States* (2021) BTWC Meeting of Experts MX2—Review of Developments in the Field of Science and Technology Related to the Convention, 2 September. Text taken from an automatically generated transcription provided by the UNOG, available at https://meetings.unoda.org/section/bwc-mx-2020-mx2/.

> clear area of overlap there, in fact the overlap goes a bit further because the interpretive statements that have been adopted over the years by the Review Conferences have made clear that the BWC also…captures synthetic analogues of toxins, regardless of the method of production…. So there are a whole series of chemical compounds that may not be natural in origin, but have similar modes of action, that would be a violation of the Biological Weapons Convention as well as the Chemical Weapons Convention. We at least see this overlap as a good thing, not a bad one, and it certainly ensures that there are no gaps.

Such clarifications as to the broad coverage of the BTWC are welcome. However, there do remain 'open questions' with regard to the application of the Convention by certain States, including the US, with regard to certain toxin categories, for example, capsaicinoids and their synthetic analogues, as explored in Chap. 8 of this publication.

9.4.3 Scope of Activities Regulated

Article I prohibits a range of activities involving biological agents and toxins except those that can be justified for prophylactic, protective, or other peaceful purposes. During the *travaux préparatoires*, States Parties clarified the term 'prophylactic' as including medical activities, such as diagnosis, therapy, and immunisation, and also agreed that 'protective' activities would cover the development of protective masks and clothing, air and water filtration systems, detection and warning devices, and decontamination equipment, and that these applications must not be interpreted as to permit possession of biological agents and toxins for defence, retaliation, or deterrence.[110] There has, however, been no such definition agreed for 'other peaceful purposes',[111] though Goldblat believed that "one can assume that it includes scientific experimentation."[112] Although these phrases have been used in BTWC Review Conference *Final Declarations*, no Extended Understandings as to their meaning have been agreed at

[110] Goldblat, J. (1997) The Biological Weapons Convention: An Overview, *International Review of Red Cross*, **79**, Article number 318, 30th June. Available at https://www.icrc.org/en/doc/resources/documents/Article/other/57jnpa.htm.; Sossai, M. (2010) Drugs as weapons: disarmament treaties facing the advances in biochemistry and non-lethal weapons technology, *Journal of Conflict & Security Law*, **15**, 5–24. p. 5.

[111] Goldblat, J. (1997) op. cit.; Sossai, M. (2010) op. cit. p. 5.

[112] Goldblat, J. (1997) op. cit.

these Review Conferences. These ambiguities have led to concerns by some commentators that biodefence programmes may potentially be employed to mask prohibited activities. This has become particularly apparent in the discussions around certain US "threat assessment" development activities which came close to, and some believe did cross the line to violating the BTWC, as explored in Chap. 8.

A further closely related issue not given adequate clarity in Article 1 or elsewhere in the Convention concerns research directly involving biological and toxin warfare agents or with regard to potential weapons, equipment, or means of delivery, and the dividing line between such research and actual weapons development. No explicit guidance is given in the Convention or in subsequent Extended Understandings to enable States Parties to determine if and when such research should be prohibited. Similarly, there are no adequate regulatory, transparency, or other measures in the Convention or developed subsequently that provide States with sufficient confidence that dual-use research conducted in another State is not being employed in the development of biological and toxin weapons or misused for other malign purposes (as explored in a number of the country case studies of this publication).

Further ambiguity surrounds application of the Article I prohibition on "weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict". Although "armed conflict" is a well-defined and understood term in international humanitarian law,[113] the application of Article 1 with regard to "hostile purposes" not amounting to "armed conflict" has not been clarified. Specifically, it is unclear how the use of toxin and bioregulator weapons for military operations other than war (MOOTW) including counter-insurgency operations, peace-enforcing and peace-keeping operations would be regulated by the BTWC. Guidance on the application of the BTWC in these areas would be beneficial including clarity on the scope of any permitted activities, the range of toxins and bioregulators (if any) that could be employed and the constraints upon such use in such circumstances.

[113] In an authoritative review of international humanitarian law, Henckaerts and Doswald-Beck, consider that "[S]tate practice establishes this rule [the use of biological weapons meant to affect humans is prohibited] as a norm of customary international law applicable in both international and non-international armed conflicts."; Henckaerts, J. and Doswald-Beck, L. (2005) *op.cit.* p. 256.

An additional area where greater clarity from the BTWC States Parties would be beneficial is the development and use of weapons employing toxins and bioregulators for law enforcement purposes. Whilst "law enforcement" would appear to fall within the ambit of "other peaceful purposes", clarity is needed on the scope of such permitted activities, the range of toxins and bioregulators that could be employed and the constraints upon such use. Although these issues have not been formally addressed at BTWC Review Conferences, the situation with regard to the development and use of certain toxin-based RCAs for law enforcement activities seems to be established, given the substantive State Practice in this area. The employment of capsacinoids and chemically synthesised analogues is widespread amongst law enforcement agencies around the world and does not appear to have been raised publicly as an issue of concern in the context of the BTWC by any State Party. The acceptability of toxin-based RCA use in a specific instance would depend on the type and quantity of agent employed, as well as the context. In contrast, the permissibility under the BTWC of research, development, stockpiling, and use of so-called incapacitating chemical agent or CNS-acting weapons employing toxins, bioregulators, other biologically active peptides, whether of natural origin or their synthetic analogues, is currently unclear and is likely to be highly contested by BTWC States Parties. Whether, when, and how this issue is raised and addressed is likely to be heavily influenced by the speed and manner in which CWC States Parties implement the 2021 CSP Decision to prohibit use of aerosolised CNS-acting chemicals for law enforcement purposes.

9.4.4 Measures to Facilitate Implementation, Verification, and Compliance

Important long-standing limitations on the value of the BTWC (and its control regime) as a tool to prevent and respond to development and use of toxin and bioregulator weapons arise from its current lack of effective verification and compliance mechanisms and the absence of an international organisation comparable to the OPCW to coordinate such activities and facilitate implementation by States Parties.

To address these significant shortcomings, in 1995, BTWC States Parties initiated a process to develop a legally binding Protocol to the BTWC that would have established an implementation body and created a verification system and other institutional structures to manage the

implementation of the Convention at the international level. However, in July 2001, just as the negotiations were nearing conclusion, the US unilaterally withdrew its support and the negotiations collapsed.[114]

9.4.4.1 Confidence-Building Measures

During the 1980s the States Parties established a range of politically binding confidence-building measures (CBMs) to facilitate transparency and information exchange concerning certain activities and facilities that might raise compliance questions. In 1991 these CBMs were further strengthened with the adoption of a new format for annual CBM reporting. This included a "[D]eclaration of past activities in offensive and/or defensive biological research and development programs" and also an "[E]xchange of information on national biological defense research and development programs."[115] Further developments in the forms used and in the submission process have been made since then. The CBMs potentially provide an important mechanism for States to alleviate concerns regarding their toxin and bioregulator research and address any misconceptions into the nature and purpose of specific research programmes. However, their effectiveness has to date been limited, given their voluntary nature; although the number of States submitting CBMs has steadily grown from 17 in 1987, only 92 of the 183 States Parties submitted CBMs in 2021.[116] Furthermore, without a process of external peer review the veracity of such information cannot be confirmed. Finally, given the extremely low level of public transparency in this area—with, for example, only 32 States publishing their CBM reports in 2021 (and some of these being redacted versions of the full CBM report circulated to States)—public knowledge and confidence in such State reporting is extremely limited.[117] In 2021, during the third strand of the Meetings of Experts (MX3) dealing with Strengthening National Implementation, there have been discussions on improving the

[114] Whitehair, R. and Brugger, S. (2001) BWC Protocol Talks in Geneva Collapse Following U.S. Rejection, *Arms Control Today*, September.

[115] United Nations (1991) *Final Declaration of the Third Review Conference of the Parties to the BTWC, Part II, Annex to Final Declaration on Confidence-Building Measures*, BWC/CONF.III/23. pp. 13–15.

[116] United Nations, *BWC Confidence Building Measures*, Overall rate of CBM Report submissions, https://bwc-ecbm.unog.ch/ (accessed 24 February 2022).

[117] United Nations, *BWC Confidence Building Measures*, Submissions made by States Parties by year: https://bwc-ecbm.unog.ch/?field_form_year_tid=557 (accessed 24 February 2022).

CBMs and on the use of voluntary visits and peer review mechanisms to increase confidence in compliance, and these could come to fruition in agreements at the Ninth BTWC Review Conference in 2022.

9.4.4.2 Review of Science and Technology (S&T)

Following the collapse of the BTWC Verification Protocol negotiations in 2001, the BTWC States Parties started an intersessional process initially between the Fifth and Sixth Review Conference and then repeated between subsequent Review Conferences.[118] These process which comprise an annual Meeting of Experts followed by a Meeting of States Parties, provide an important mechanism which could be utilised to monitor advances in science and technology that could be applicable to the development of new forms of toxin weapons.

For example, the Seventh BTWC Review Conference decided to include, as part of its 2012–2015 intersessional programme, a standing agenda item to review developments in the field of science and technology related to the Convention.[119] Consequently, in 2014: "advances in the understanding of pathogenicity, virulence, toxicology, immunology and related issues" were reviewed; whilst in 2015 "advances in production, dispersal and delivery technologies of biological agents and toxins" were considered.[120] Such structured reviews by the BTWC States Parties present important opportunities for individual States Parties and civil society to highlight research and development trajectories of potential concern, including those relating to the development of toxin and bioregulator weapons. For example, in 2016 at the Eighth Review Conference, the UK submitted a paper[121] that attempted to summarise the discussions on

[118] United Nations (2002) Fifth Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. *Final Report*, BWC/CONF.V/17. United Nations, Geneva, December.

[119] United Nations (2011) Seventh Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. *Final Document of the Seventh BTWC Review Conference*. BWC/CONF.VII/7. Decisions and Recommendations, paragraph 8(b).

[120] United Nations (2011) *Final Document of the Seventh BTWC Review Conference*. op. cit. Decisions and Recommendations, paragraph 23 (c) and 23 (d).

[121] United Kingdom (2016) *Review of Developments in Science and Technology: Key Points from the 2012–2015 Biological and Toxin Weapons Convention Intersessional Programme*. BWC/CONF.VCIII/WP.17. United Nations, Geneva, 1 November. p. 7.

science and technology since the Seventh Review Conference and concluded that one of the seven issues requiring further consideration in an enhanced review mechanism was:

> (d) **developments derived from the convergence of biology, chemistry and other scientific disciplines**, for example: advances in neuroscience, including design and delivery of peptides and other neurotransmitters; trends in production processes, including for toxins and bioregulators; nanotechnology, including its application to defensive countermeasures, such as detection and diagnosis, protective clothing and equipment, medical countermeasures and decontamination. This could include exploring appropriate ways and means to promote greater collaboration with the CWC to analyse potential benefits, risks and threats resulting from relevant advances in science and technology. (Original emphasis)

The importance of the BTWC establishing effective mechanisms to review relevant science and technology developments, including those relating to toxins and bioregulators, is underscored by growing concerns that continuing biotechnological development will lower the technological barriers to toxin weaponisation. In its November 2021 analysis of science and technology trends of relevance to the BTWC, the US stated:

> Rapid advances in science and technology have expanded the ability to manipulate biological agents and toxins, potentially enabling production and delivery or allowing for more facile engineering of agents with enhanced characteristics. For instance, some toxins that exist in nature have traditionally been considered to have a low likelihood of weaponization because of a limited ability to isolate the toxin from its host microbe. Today, several of those toxins can be produced in higher quantities, using genetic engineering or chemical synthesis techniques, thus making them more accessible as a potential weapon.[122]

At the present time there remain questions over what the science and technology review mechanism should do and how it should be organised. As set out in a study by the United Nations Institute for Disarmament

[122] United States (2021) *Current Trends and their Implications to the Biological Weapons Convention*. 2020 Meeting of the States Parties to the BTWC, Geneva, 22–25 November 2021. BWC/MSP/2020/WP.12, 21 November.

Research (UNIDIR) in late 2020,[123] these included: "[W]hat should this mechanism do? Who should be the primary audience for outputs? Who should determine specific priority areas (and how)? How many participants should be involved? What form of institutional support is required?" However, these issues are being worked on intensively and could result in an agreement on a new review mechanism at the 9th Review Conference.

9.4.4.3 Implementation Support Unit

A significant limitation of the BTWC is the current lack of sufficient institutional support to encourage and facilitate effective implementation of the Convention by all State Parties. Instead there is a three-person BTWC Implementation Support Unit (ISU) within the UNODA of the United Nations Office at Geneva. The ISU was established after the Sixth Review Conference in 2006 to provide administrative support to meetings agreed by the Review Conference as well as comprehensive implementation and universalisation of the Convention and the exchange of confidence-building measures.[124] Its mandate (and funding) has been repeatedly renewed and extended by successive Review Conferences and will currently run until 2022.[125] It is to be hoped that there will be an increase in the number of people in the ISU agreed at the 9th Review Conference and in particular that there is agreement to appoint a person with specific responsibility for monitoring and facilitating State Party measures to address scientific and technological change.

9.4.4.4 Non-compliance Measures

Although lacking formal verification measures, the BTWC does contain two Articles that were intended to address non-compliance concerns by other means. Article V encouraged States Parties to "consult one another and to cooperate in solving any problems which may arise in relation to

[123] Anand, A. and Revill, J. (2020) *Exploring Science and Technology Reviews Under the Biological and Toxin Weapons Convention (BWC)*. Presentation at a S&T Review Mechanisms Workshop, 9 December, 2020. Available under MX2 at the UNODA Meetings Place, Geneva.

[124] For further details of the key tasks of the ISU see: United Nations, Implementation Support Unit, UN Office for Disarmament Affairs, https://www.un.org/disarmament/biological-weapons/implementation-support-unit (accessed 8 November 2021).

[125] United Nations (2011) *Final Document of the Seventh BTWC Review Conference*. op. cit. Decisions and recommendations, Implementation support unit, paragraph 31; United Nations (2016) *Final Document of the Eighth Review Conference*, BWC/CONF. VIII/CRP.2, III, B, paragraph 3.

the objective of, or in the application of the provisions of, the Convention".[126] Although these provisions have been employed by States Parties, such bilateral consultations are necessarily confidential in nature, and consequently, it is difficult for civil society to ascertain how frequently such consultations have been utilised and how effective they have been. As well as such bilateral consultations, Article V also allows for consultations to be conducted on a multilateral basis "through appropriate international procedures within the framework of the United Nations and in accordance with its Charter".[127] At the time of writing, this provision has been utilised once, resulting in a consultative meeting in 1997.[128]

In addition, Article VI of the BTWC allows any State Party to lodge a complaint with the United Nations Security Council (UNSC) about non-compliance by another State Party. The UNSC may then launch an investigation, with which all parties are enjoined to cooperate.[129] Such investigations would be conducted by the UN Secretary-General utilising the resources and capabilities available to them, including the UNSGM detailed earlier, and would cover suspected use of toxin or bioregulator weapons in all forms of armed conflict, and potentially also the use of such weapons to commit human rights abuses in the absence of such armed conflict.[130]

9.5 Conclusions

It is clear that toxins and bioregulators come under the scope of the Geneva Protocol, the BTWC and the CWC. However, the manner in which they have been addressed, the delineation of prohibited and regulated activities, and the consequent obligations upon States Parties differ, as does the strength of, and resources allotted to, implementation, transparency, verification, and compliance measures. Such differences have

[126] *Biological and Toxin Weapons Convention* (1972) op. cit., Article V.

[127] *Biological and Toxin Weapons Convention* (1972) op. cit. Article V.

[128] For further discussion see: Tucker, J. (2011) *Strengthening Consultative Mechanisms Under Article V to Address BWC Compliance Concerns, Harvard Sussex Program*. May. Available at op. cit. http://www.sussex.ac.uk/Units/spru/hsp/occasional%20papers/HSPOP_1.pdf. pp. 8–9.

[129] *Biological and Toxin Weapons Convention* (1972) op. cit. Article VI.

[130] If the Security Council decides it wants an investigation and tasks the Secretary-General to conduct such an investigation, the SG would have the freedom to use the resources and capabilities available to him, and that would include the UNSGM. However, investigation of human rights abuses would not be part of a BTWC process.

important consequences for the utility of each instrument in facilitating effective regulation of toxin and bioregulator research, associated activities of potential concern, and the broader prevention of development and use of toxin and bioregulator weapons.

The Geneva Protocol prohibits the use in war of biological and chemical weapons (including toxins and bioregulators) against plants as well as animals and humans. This narrow normative prohibition was the essential bedrock upon which the more comprehensive prohibitions established under the BTWC and CWC could be built. Crucially, the Geneva Protocol's constraints which have become established as customary international law are applicable on all States—even those not party to the BTWC or CWC, or which subsequently withdraw from these treaties. However, because its prohibitions relate solely to use, the Geneva Protocol has no direct utility in regulating dual-use research and development of toxin and bioregulator weapons.

The BTWC under its Article 1 GPC, and through Extended Understandings agreed at successive Review Conferences, makes clear that the Convention is comprehensive in scope and covers both naturally occurring and synthetic toxins and bioregulators. Furthermore, the development, production, acquisition, stockpiling, and use of toxins and bioregulators other than for prophylactic, protective, or other peaceful purposes are prohibited. As with the Geneva Protocol, but unlike the CWC, the BTWC prohibitions cover weaponised agents intended to attack plants, as well as animals and humans. However, there are a number of long-standing ambiguities and limitations in the Convention that its States Parties have failed to address. These include failing to: define toxins and clarify the range of substances covered by this term; determine whether toxin and bioregulator weapons can be developed and employed for use in law enforcement and if so, what types, in what circumstances and under what constraints; address how dual-use research can be regulated in accordance with the Convention to ensure it does not directly facilitate or is not employed in the development of toxin and bioregulators for prohibited purposes. In addition, it must also be recognised there are important long-standing and systemic weaknesses that severely limit the value of the BTWC as a tool to prevent and address the development of toxin and bioregulator weapons. These include the current lack of effective transparency, verification, and compliance mechanisms; inadequate monitoring and review of advances in relevant science and technology; and also the absence of a sufficiently resourced international organisation empowered to coordinate such activities and to facilitate effective implementation by States Parties.

The CWC through its definitions of "toxic chemicals" and "chemical weapons" incorporating a GPC, ensures a comprehensive and essentially open coverage of substances within its scope including all existing and yet to be discovered or synthesised toxins and bioregulators. While the CWC prohibits the development and use of all chemical weapons against animals and humans, it permits the use of toxic chemicals including toxins and bioregulators for a range of "purposes not prohibited" notably law enforcement, but only "as long as the types and quantities are consistent with such purposes." The CWC specifically lists two toxins in its Schedules of chemicals requiring specific regulation and subject to routine verification measures; and an additional six capsaicinoids and one synthetic analogue that are considered to be riot control agents and can be employed in law enforcement, but are prohibited for use in armed conflict. The application of the Convention in certain relevant areas is contested including the appropriate regulation of dual-use research for "protective purposes", and the legitimacy of research, development, and use of law enforcement CNS-acting weapons, despite the welcome CSP-26 Decision banning the aerosolised use of CNS-acting chemicals in law enforcement. The application of the Convention in other areas, notably to malodorants and wide area RCA means of delivery, has not been formally raised by States Parties in any OPCW policy-making organ.

From this analysis, it is clear that the texts of both the BTWC and the CWC suffer from significant ambiguities and limitations affecting the regulation of toxins and bioregulators that have not been addressed by the States Parties. Consequently, the apparent overlap of the BTWC and CWC regimes' scope with regard to toxins and bioregulators in practice currently masks a regulatory gap, with neither Convention being effectively implemented to ensure these substances are not developed as weapons. Comparing both Conventions, it is evident that despite its limitations, the CWC does contain a range of existing mechanisms that could be strengthened and effectively applied to regulate toxins and bioregulators, if States Parties were willing. Consequently, it appears that the OPCW provides the best opportunities in the short to medium term for regulating bioregulator and toxin dual-use research and associated activities of concern to ensure that they are not, and are not perceived to be, exploited for malign purposes.

CHAPTER 10

Conclusion and Recommendations

10.1 Introduction

In Chap. 1 we highlighted how the rapidly advancing and converging chemical, life, and associated sciences raise new challenges for States in their attempts to regulate toxin and bioregulator dual-use research and prevent its misuse for malign purposes. We described how such substances come under the scope of both the Chemical Weapons Convention (CWC) and the Biological and Toxin Weapons Convention (BTWC), and our concern that rather than being effectively regulated by both overlapping Conventions they actually are neglected by both, as the CWC is largely focused on synthetic chemical agents and the BTWC is focused on pathogenic microorganisms. We explained how this regulatory gap could result in a failure of either regime to prevent the employment of dual-use toxin and bioregulator research and associated activities in weapons programmes. In addition to the consequences of failing to address actual weaponisation, we highlighted how the growth in misperceptions and misunderstandings over benignly intended dual-use research could erode confidence in both the BTWC and the CWC.

In Chap. 2 we argued that a very significant change has come about in the chemical, life, and associated sciences that will progressively allow a more and more mechanistic understanding of the operation of living biochemical systems and that while this will enable us to deal more effectively with dangerous diseases, it could also greatly enhance the potential for

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_10

malign development of novel chemical and biological agents—including toxins and bioregulators. We then described some key toxins and bioregulators, that have or could prove to be candidates for malign application, in more detail and demonstrated how quickly our understanding of these agents, and their effects is advancing. Chapters 3, 4, 5, 6, 7, and 8 dealt with our studies of these issues in China, India, Iran, Russia, Syria, and the US. Chapter 9 then reviewed in more detail how toxins and bioregulators—and related substances of biological origin (and their synthetic analogues) that could arguably be considered as toxins—as well as associated means of delivery, are regulated by the CWC, the BTWC, and other international agreements. This included analysis of certain riot control agents, malodorants and incapacitating chemical agents.

In this chapter we begin by summarising the main findings of our country case studies, draw out what we see as the overarching themes that arise from our research, and finally make recommendations about how the main problems that we have identified might be remedied.

10.2 Country Case Studies

Certain lines of contemporary research into a range of toxins and bioregulators, synthetic analogues, and associated bioregulatory pathways could potentially be—rightly or wrongly—construed as being linked to the study or development of biological and chemical weapons. The following six country case studies, developed from research employing a standardised methodology, sought to explore a variety of different scenarios and contexts in which contemporary research, potentially applicable to toxin and bioregulator weapons, has reportedly occurred, or where such weapons have reportedly been developed prior to and since the coming into force of the BTWC and CWC. The case studies also examined how the six States have reported on relevant research and associated activities to address potential concerns or misinterpretations that such activities were for malign intent.

10.2.1 China

Certain States and commentators have asserted that China previously had a biological and toxin weapons programme which it has not declared and which they claim may not have been fully dismantled. China strongly rejects these accusations. Open-source information indicates that a range of contemporary toxin and bioregulator research, of possible dual-use

application, has been carried out by military and military-related institutions and researchers. This has included work on 'classic' toxin agents such as botulinum, ricin, staphylococcal enterotoxin B (SEB), and shiga, as well as 'novel' toxins obtained from sea anemones, jellyfish, salpa, shellfish and scorpions. Further dual-use research has been undertaken under the China Brain Project and associated work on neurological systems and associated bioregulators, employing animal models including non-human primates. Whilst certain such research has clear medical or protective applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied. China has submitted BTWC Confidence Building Measure (CBM) reports and CWC (Article X) Declarations of national programmes related to "protective purposes". As civil society does not have access to either China's BTWC CBM reports nor its CWC Article X Declarations, it is not publicly known whether and if so, how dual-use research highlighted in this study has been reported to BTWC and CWC States Parties.

Additional dual-use concerns relate to the development by Chinese State companies of a range of 'wide area' riot control agent (RCA) means of delivery. A number of these are potentially capable of disseminating toxin-based RCAs over large areas or extended distances. Chinese State companies have also developed central nervous system (CNS)-acting weapons for use against individuals and such weapons have been documented in the possession of the Chinese Peoples' Liberation Army. Whilst both categories of weapons have purportedly been developed for law enforcement, it is uncertain whether their use for such purposes would be safe and appropriate.

10.2.2 India

Indian military and military-related and funded institutions and scientists have recently searched for, identified, and characterised toxins and other substances from a broad range of indigenous Indian stinging and other poisonous plants. Contemporary scientific papers published by these researchers describe their work as being associated with the potential "formulation of novel future bio-threat agents for self-defence" or alternatively of being "exploited for the development of novel multisystem targeted agents for self-defence". Some of the toxins investigated as potential agents are highly

toxic and could be lethal; others though not as toxic could still potentially be employed as "less lethal" toxin weapons. In scientific publications describing their research, authors from Indian military institutions have claimed that such activities are permitted under the BTWC, although this interpretation appears to be a misreading of the Convention. Since 2009, India has submitted BTWC CBM reports on an annual basis. It is not publicly known whether and how frequently India submits CWC (Article X) Declarations of national programmes related to "protective purposes". As civil society does not have access to either India's BTWC CBM reports nor its CWC Article X Declarations, it is not publicly known whether and if so, how the research highlighted in this study has been reported to BTWC and CWC States Parties. It is not possible, from the available open-source information, to assess whether these activities are consistent with India's obligations under the BTWC and CWC, though the information currently available raises concerns that this may not be the case.

Additional dual-use concerns relate to the development or acquisition by Indian law enforcement bodies of 'wide area' RCA means of delivery capable of disseminating these agents (potentially including toxin-based RCAs) over large areas or extended distances. Whilst these weapons are purportedly intended for law enforcement, it is unclear whether the use of certain weapons for such purposes would be safe and appropriate. Indian scientists, including those associated with the DRDO, have undertaken research into a range of malodorants apparently with the intention of developing them for use in law enforcement crowd dispersal operations. DRDO scientists have also undertaken research into pharmaceutical chemicals that could have dual use applications in relation to ICA/CNS-acting agents.

10.2.3 Iran

While Iran has formally declared that it rejects development and use of "weapons of mass destruction", some past statements by high-level Iranian officials appeared to indicate an intention to develop chemical and biological weapons, and certain States have alleged that Iran did have, and/or may have, a biological weapons programme. Open-source information indicates that a range of contemporary toxin and bioregulator research of possible dual-use application has been carried out, including by Iranian military-related institutions and researchers. This has included work on 'classic' toxin agents such as botulinum, ricin, SEB, and T-2 and 'novel' toxins derived from scorpion and box jellyfish venom; and bioregulators including substances that interact with gamma-aminobutyric acid (GABA) receptors.

Whilst certain such research has clear medical or protective applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied. Although Iran has submitted BTWC CBM reports, such reporting has been infrequent. It is not publicly known whether and how frequently Iran submits CWC (Article X) Declarations of national programmes related to "protective purposes". As civil society does not have access to either Iran's BTWC CBM reports nor its CWC Article X Declarations, it is not publicly known whether and if so, how dual-use research highlighted in this study has been reported to BTWC and CWC States Parties.

Iranian scientists have conducted research into pharmaceutical chemicals that could have dual-use application in relation to ICA/CNS-acting agents. At least one Iranian company has reportedly developed a 'wide area' means of delivery capable of disseminating RCAs (potentially including toxin-based RCAs) over large areas.

10.2.4 Russia

The former Soviet Union had an enormous clandestine biological weapons programme during the past century, and this reportedly included work to develop toxin and bioregulator weapons. Moreover, Soviet scientists reportedly explicitly argued that development and use of bioregulator weapons was not prohibited by the BTWC. The former Soviet biological weapons programme was closed down, along with the chemical weapons programme, in the early 1990s, and the declared chemical weapons stockpile was verifiably destroyed in 2017. However, certain States have raised repeated concerns as to whether Russian research and development of biological and toxin weapons subsequently continued. These concerns were deepened due to lack of access to and transparency concerning certain Russian facilities previously involved in Soviet biological weapons development, as well as ambiguous Russian statements concerning new "genetic weapons". In 2020 the US declared that Russia maintains an offensive biological weapons programme and enacted sanctions against certain Russian research institutions.

Open-source information indicates that a range of contemporary toxin research of potential dual-use application has been carried out including by institutions that were associated in various ways with the former Soviet

biological weapons programme. This has included work on 'classic' toxin agents including botulinum, as well as 'novel' toxins such as epibatidine (derived from poisonous frogs), and poisonous and hallucinogenic molecules derived from fungi. Since 1987, Russia has submitted BTWC CBM reports on an annual basis. It is not publicly known whether and how frequently Russia submits CWC (Article X) Declarations of national programmes related to 'protective purposes'. As civil society does not have access to either Russia's BTWC CBM reports nor its CWC Article X Declarations, it is not publicly known whether and if so, how the research highlighted in this study has been reported to BTWC and CWC States Parties. Whilst certain such research has clear medical, protective, or other legitimate applications, given the corresponding lack of public reporting and transparency, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied.

The Soviet Union undertook research and development of a range of CNS-acting weapons, including those employing pharmaceutical chemicals, toxins, and bioregulators. In 2002 Russia employed an aerosolised CNS-acting pharmaceutical chemical weapon in a large-scale anti-terrorist operation. It is unknown whether research and development of toxin and bioregulator CNS-acting weapons has been undertaken by Russia and whether stockpiles of such agents remain. Russia currently maintains that the law enforcement use of CNS-acting weapons is not regulated by the CWC. Additional concerns relate to the previous reported development by at least one Russian company of delivery mechanisms capable of disseminating RCAs over large areas or extended distances. A number of these could potentially deliver or be adapted to deliver OC and its synthetic analogues. From publicly available information they appear to be inconsistent with the CWC and potentially the BTWC.

10.2.5 Syria

In July 2012 the Syrian government seemed to imply that it possessed both biological and chemical weapons, although it provided no details of the nature or scale of its holdings. In October 2013 it acceded to the CWC, subsequently declared its existing stockpile of chemical weapons, and agreed to facilitate their verification and subsequent destruction under the supervision of the OPCW. This initial declaration apparently contained either no information or incomplete information regarding Syria's toxin-related activities. Concerns were raised by certain States Parties about the accuracy and completeness of Syria's initial declaration—including in

regard to potential ricin production. Syria submitted an amended declaration stating it possessed a Chemical Weapons Production Facility (CWPF) but that all ricin stocks had been destroyed prior to entry-into-force of the Convention.

In July 2018, the OPCW verified the destruction of the Al-Maliha ricin production facility. No public information is available concerning the size and nature of the facility, the amount of ricin produced, when ricin stockpiles were destroyed, by whom, nor crucially what was the intended purpose behind this ricin production. Syria has never publicly admitted that the ricin produced at Al-Maliha was for use in toxin weapons, instead it reportedly claimed that the ricin was destined for medical purposes. Certain States, notably the UK, however subsequently maintained that the ricin was intended for weaponisation and that Syria had acknowledged this. Given previous repeated obfuscation of its chemical weapons programme, there is legitimate concern as to whether Syria has been completely forthright over its activities at Al-Maliha, and whether any further production facilities or stockpiles of ricin or other potential toxin weapons remain.

10.2.6 US

The US formally initiated a biological weapons programme during World War II. This programme, including work to develop toxin weapons, was closed down at the beginning of the 1970s. The US chemical weapons programme, which began in 1917, was renounced in 1991. Comprehensively verified destruction of all remaining US chemical weapons stockpiles, initiated following its accession to the CWC in 1997, is ongoing. There has been a long series of concerns raised over decades about military-funded and military-related US institutions reportedly carrying out biological weapons-related research for ‘defensive purposes’ which have been perceived by certain States and civil society observers as potentially crossing the line into offensive weapons research. Particular concerns related to the apparent questionable US interpretation that the BTWC allows development of biological weapons when intended for threat assessment and developing defensive counter-measures.

Open-source information indicates that a range of contemporary toxin and bioregulator research, of possible dual-use application, has been carried out by US military and military-related institutions and researchers. This has included investigation of staphylococcal superantigen functioning; production of engineered non-toxic botulinum toxins through

'rational design'; employment of recombinant technology to develop a non-toxic SEB mutant; and work on aerosolised ricin and aerosolised botulinum toxin. The US has provided sufficient information or allowed public reporting and publication of scientific papers on much of this research indicating their medical or protective purpose. However, given the lack of full public reporting and transparency for certain facilities and programmes, it is not possible to determine the purposes for which all such research has been undertaken or to which it will be applied. Given limited transparency in this area, it is not publicly known whether and how frequently the US provides CWC Article X declarations to the OPCW and whether they include details of toxin and bioregulator research for 'protective purposes'. In contrast, the US is one of only a minority of States that have made their BTWC CBM reports available to the public, albeit in a redacted form.

The US conducted long-term research into a range of potential incapacitating chemical agents (or CNS-acting chemicals), including pharmaceutical chemicals and bioregulators, and related bioregulatory pathways, for law enforcement and military purposes, on and off from the 1970s through to the early years of this century. In addition to military- and law enforcement-funded projects directly intended to inform or facilitate the development of such weapons, a wider range of potentially relevant dual-use research into related fields such as the US Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative has been funded in part by the US Department of Defense. In 2013 the US stated that it rejected the development, stockpiling, and use of incapacitating chemical agent/CNS-acting weapons, a position it reconfirmed in 2022.

US defence and defence-funded projects have researched and explored development of malodorant weapons apparently investigating both naturally occurring substances and synthetic chemicals. The US military also undertook or funded projects to develop a variety of delivery and dispersal mechanisms. Certain US companies have promoted malodorants and associated means of delivery to the law enforcement and military communities. The US military has given conflicting indications of how it considers malodorants to be regulated under the CWC. It previously argued that malodorants were not restricted by the CWC because they did not rely on their toxic properties to exert their effects; subsequent US military statements indicate that it does not consider at least certain malodorants to be RCAs.

Additional dual-use concerns relate to the development by US companies of 'wide area' RCA means of delivery, a number of which are potentially capable of disseminating the toxin-based RCA, oleoresin capsicum (OC) and its synthetic analogues, over large areas or extended distances. Concerns are exacerbated by the long-held US interpretation of the CWC that though RCAs (including OC) cannot be used as a "method of warfare", they may be legitimately used by US military in certain armed conflict contexts, including where civilians are used to mask or screen attacks, or to protect convoys from paramilitary organisations. Furthermore, US military legal experts have previously argued that OC falls outside the scope of the BTWC.

10.3 Overarching Themes

10.3.1 The Revolutionary Changes, Convergences, and Interactions Between Chemical, Life Science, and Associated Science and Technology

A range of national and international scientific and medical bodies have highlighted the continuing rapid and revolutionary changes that have taken place in relevant life and chemical scientific disciplines and technologies over the past 30 years and have explored the potential likelihood for, and the implications of, the misuse of such research. Of particular potential relevance have been developments and convergences in neuroscience, medicinal chemistry, pharmacology, toxicology, immunology, molecular biology, systems biology and synthetic biology, as well as their interactions with nanoscience, artificial intelligence research and computer science. This change in technological capabilities has had practical implications for those concerned about the dangers of novel weapons development. As Julian Perry Robinson pointed out: "[B]ecause of…convergence of chemistry and biology, we may eventually be able to manipulate at will the processes of development, inheritance, reproduction, locomotion, sensation, cognition and any other process that keeps us working as normal human beings."[1] The potential effects of such scientific and technological developments are amplified and influenced by the continuing growth and

[1] Perry Robinson, J. (2008) Bringing the CBW Conventions Closer Together. *The CBW Conventions Bulletin*, **80**, 1–4. p. 2.

patterns of globalisation of commercial biotechnological and chemical industries, the increased availability of materials, and the 'democratisation' of expertise arising from trade and communications.

In Chap. 2, and also through the country case studies, we sought to explore how such changes were affecting the scientific fields related to the discovery and study of toxins and bioregulators, their mechanisms of action, the corresponding receptor and sub-receptor sites they interact with, and the broader functioning of the human brain, central nervous system, and other regulatory and physiological systems they affect. Such advances have gone in parallel with the increasing ability to chemically synthesise peptide bioregulators and incorporate chemical modifications resulting in analogues with markedly different physiological properties. All this knowledge is likely to provide significant benefits to society; however, given its multi-faceted applicability, these advances could also potentially be exploited for military and law enforcement applications, including the development of toxin and bioregulator weapons.

In addition to discovery or synthetic development of candidate toxins, bioregulators, and their analogues, and analysis of the physiological pathways on which they will act, those seeking to employ such agents as weapons must also overcome the challenge of ensuring their controlled delivery to the target population. Two factors influence such agent delivery: dissemination—the transport of the agent from the attacker to the immediate vicinity of the targeted person or persons; and, uptake—the taking in and subsequent movement of the agent to its active site within the target.

With regard to agent uptake, the implications of developments in particle engineering and nanotechnology that could allow the delivery of biologically active chemicals to specific target organs or receptors have been highlighted by a number of scientific bodies. Of particular concern has been the employment of nanotechnologies that could be used to overcome the blood-brain barrier and thereby enable unparalleled access to the brain. With regard to agent dissemination, rapid advances in aerosol technology that have already been employed to deliver effective inhaled drug therapy for the treatment of disease could be instead adapted for the malign delivery of agents. Of potentially greater long-term concern are the application of developments in nanotechnologies and gas-phase techniques that could provide improved means of dispersal of weapons agents over wide areas. Such concerns are exacerbated by the current development, production, and commercial availability of an extensive range of delivery mechanisms marketed for the dispersal of RCAs (including toxin-based RCAs) some of which could be utilised or adapted for delivering

other toxic chemicals, potentially including weaponised toxins and bioregulators.

10.3.2 Implications of Research Shifts from Potential Agents to Potential Targets

Twenty years ago, Petro and his colleagues suggested that advances in the life and associated sciences could lead to a paradigm change in regard to biological weapons development: they suggested that the focus would move from studies of the possible agents to studies of the vast number of novel potential targets that would become known.[2] This 'game changer' has become ever more likely as the ability to combine experimental data with mathematical analysis and powerful information technology in the systems biology approach has increased the capability to predict the responses of biological entities to particular stimuli. This approach is particularly relevant to studies of the effects of toxins and bioregulators on living organisms; this was illustrated by our examination in Chap. 2, of how the complex interactions within the immune system, and linked nervous and endocrine systems, are affected by toxins and bioregulators. As was pointed out by Nixdorff in a recent review of the implications of systems biology for the BTWC and the CWC:

> Biochemical bioregulators are relevant agents of concern for both [Conventions]. However, the expansion of the threat spectrum into new categories of agents has not yet received proper consideration in the deliberations within either convention on how to come to grips with the dual-use issues involved, or in the actual formulation of national or international oversight policies.[3]

As the author added, while this expansion of the threat spectrum to include bioregulators was dealt with in the Lemon-Relman report of the US National Academies in 2006, there has been "little effort to formulate security policies so as to extend the seven categories of dual-use research of concern as defined by the earlier Fink Committee to include experiments with biochemical regulators in the context of systems-biology

[2] Petro, J. B. et al. (2003) Biotechnology: Impact on biological warfare and biodefense. *Biosecurity and Bioterrorism*, **1**, 161–168.

[3] Nixdorff, K. (2021): Developments in systems biology: implications for health and biochemical security, *The Nonproliferation Review*, DOI: 10.1080/10736700.2020.1865632. p. 13.

research."[4] We agree with this view and with the author's concern that scientists working in this field need more help along the lines suggested, such as to add to the Fink Committee's well-known list of experiments of concern,[5] the further topic "experiments that would demonstrate ways of using bioregulators (neurotransmitters/neuropeptides, hormones or cytokines) to modify the balanced function of vital physiological processes in negative ways."[6] This suggestion refers back to the infamous mousepox experiment at the turn of the century.[7] In this experiment Australian civil researchers began by altering a mousepox virus, incorporating an additional mouse egg protein gene intended to produce the egg protein and thus act as a contraceptive in infected mice. Their aim was to induce an immune response to mouse eggs in the infected mice and so reduce mouse fertility and decrease the mouse population (which is considered a pest in Australia). The immune response was not strong enough so they also added the gene for a cytokine of the immune system to the virus which they thought would increase the immune response in the infected mice. However, the addition of the cytokine upset the balance of positive and negative factors in the immune control system and destroyed the response to the virus in infected mice—thus turning the virus into a mouse killer. It was not long before the security community recognised the possibilities for a similar modification of other pox viruses such as smallpox.

We are not aware of any proposals analogous to those of the Fink Committee for assisting scientists to think about the implications of their work in regard to bioregulators, or indeed in regard to their research on toxins. It would certainly be helpful if such kinds of guidance were developed by the scientific community. Moreover, in addition to developing and promulgating further advice and guidance for chemical and life scientists, the potential consequences of this fundamental change in focus from potential agents to potential targets, and the broader implications for national and international regulation of chemical and life science dual-use research and associated activities should be systematically explored and addressed. For example, should a similar amount of attention be given to

[4] National Research Council (2006) *Globalization, Biosecurity, and the Future of the Life Sciences*. National Academies Press, Washington, D.C.

[5] National Research Council (2004) *Biotechnology Research in an Age of Terrorism*. National Academies Press, Washington, D.C.

[6] Nixdorff, K. (2021) op. cit. p. 13.

[7] Jackson, J.J. et al (2001) Expression of Mousepox Interleukin-4 by a Recombinant Ectromella Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox. *Journal of Virology*, **75**(3), 1205–1210.

the possibilities of the development of destructive biochemical agents that could render the immune system ineffective as has traditionally been given to the genetic manipulation of pathogens?

10.3.3 Changing Threats and Perceived Utilities of Toxin and Bioregulator Weapons

State perceptions of the potential threats from, or utilities of, toxin and bioregulator weapons could be influenced by the unique ever-fluid and evolving international, regional, and national security environment which each State faces. Such considerations are complicated where the borders may blur and shift between large- and smaller-scale international and non-international armed conflicts, large-scale human rights violations, revolutions and uprisings, insurgencies, terrorism, and organised crime.

Of obvious concern would be potential State interest in perceived military utility and consequent development and acquisition of toxin and bioregulator weapons with wide area battlefield effects causing mass fatalities and casualties through severe disruption of the central nervous system and other core bodily functions. Alternatively, State militaries may be attracted to "less lethal" forms of such weapons causing unconsciousness, immobilisation, or other temporary incapacitation, or which more subtly alter opposing combatants' perception, emotions, and behaviour. In addition to their use in full-scale armed conflict, military forces could also employ toxin or bioregulator weapons in other scenarios of potential or actual combat such as peacekeeping, peace enforcement, counter-insurgency, or counter-terrorist operations, particularly where civilians and combatants are mixed. Other situations may include use by occupying forces to subdue restive or angry civilian populations; or in the control of unruly internees, displaced persons or prisoners of war.

Police and security forces, in addition to continued employment of existing RCAs (including the toxin-based RCA, OC, and its synthetic analogue, pelargonic acid vanillylamide (PAVA)), may be tempted to utilise toxins and bioregulators for domestic law enforcement to manipulate or punish protesting crowds or for other large-scale policing of public assemblies. In custodial situations, certain toxins and bioregulators could make prisoners, other detainees, and patients more compliant and trusting, or be used as "truth drugs" in forced interrogations. In contrast, alternative toxins and bioregulators that cause discomfort, pain or illness, or induce depression or anxiety, could be employed in torture and other cruel, inhuman, or

degrading treatment or punishment. Certain State intelligence and internal security forces have previously attempted to develop bioregulator and toxin weapons for use in espionage operations including covert assassinations, and it seems plausible that such activities will continue, potentially for use against their own citizens and targets in third countries.

Building on the existing capabilities of the chemical, life science and associated sciences and postulating potential research trajectories, one can imagine how the malign application of future developments, if insufficiently regulated, could enable States to chemically manipulate and subjugate large swathes of their own or foreign populations. Although such potential repressive capabilities are thankfully speculative at present, our rapidly increasing knowledge of, and ability to influence, the body's bioregulatory pathways, and consequently manipulate the central nervous system and other core physiological systems, coupled with advances in wide area agent dissemination and uptake, mean that such threats, if not addressed now, are likely to increase in coming years.

The BTWC and CWC were primarily intended, and had been designed, to prevent and address the development and use of biological and chemical (including toxin) weapons in armed conflict, and to facilitate the destruction of all existing weapons production capacity and stockpiles. There are questions as to how capable these Conventions and the associated control regimes are to adequately respond to the wider potential malign application of the chemical and life sciences outside of armed conflict. Furthermore, there are 'open questions' as to whether the States Parties to either or both Conventions will be collectively willing to permit the reallocation of limited resources to address these additional concerns. In such circumstances the application of other relevant international law, notably international human rights law, needs to be considered.

10.3.4 Trust, Distrust, Mistrust, and Disinformation

There have been State-level chemical and biological weapons programmes in the past and these have involved research and attempted development of toxins and bioregulators as weapons. In regard to certain of these States, there are ongoing concerns that such weapons development programmes are still operating today. Chemical and life science research institutions can have long histories and may at times have been involved in various ways with such programmes, and scientists in these institutions can have decades-long careers working in relevant fields of dual-use research during which they may cycle between participation and non-participation in such programmes.

Obviously, that historical context does not make contemporary trust-building straightforward. This is made even harder when these potentially dubious or illegal historical activities were not adequately reported, investigated, and resolved at the time by national and international oversight bodies, that is, the OPCW and/or BTWC States Parties. Such failures, if not subsequently recognised and addressed, can influence the international community's current trust or mistrust in individual chemical and life science institution activities, and the intention behind relevant State's chemical and biological weapons-related policies and practices. More broadly, such reporting, investigation, and verification failures have more diffusive, yet cumulatively significant, long-term corrosive effects upon State and civil society confidence in the current capability and resolve of the OPCW and BTWC States Parties to address contemporary activities of concern.

It is the duty of all States where they have legitimate concerns about another State's activities potentially related to the development, acquisition, or use of biological and chemical (including toxin and bioregulator) weapons, to bring their concerns to the relevant international regulatory bodies, in good faith, so that they can be investigated and resolved. Certain States, notably the US, have raised their concerns about the activities of other States (e.g. China, Iran, Russia, and Syria) potentially related to the development or possession of bioregulator and toxin weapons, and have publicly provided, albeit limited, open-source information to support their concerns. Such US allegations are normally documented in annual US assessment reports of State compliance with the BTWC and CWC, and have been included in high-level US statements to the UN and to meetings of BTWC States Parties and/or the OPCW. The US has also documented its attempts to raise these issues with the relevant States on a bilateral basis. To date, however, it appears that neither the US nor other States that have publicly voiced such toxin weapons concerns, have attempted to initiate the appropriate formal multilateral consultation, investigation, and fact-finding mechanisms under the CWC, and/or the formal multilateral BTWC consultation measures to raise and resolve these issues.[8] We recognise that outside civil society observers do not know the full extent and nature of the confidential diplomatic measures that the US and other States have undertaken to resolve their concerns with those

[8] It should be noted, however, that certain CWC States Parties have raised and sought to addresss toxin-related concerns through other means within the OPCW. See for example Chap. 7, for discussion of concerns regarding the accuracy and completeness of Syria's CW declaration including with respect to ricin, and the consequent establishment and work of the OPCW Declaration Assessment Team to attempt to resolve these issues.

States alleged to have undertaken troubling activities. And, of course, the relevant officials and diplomats are well placed to judge what the most effective strategies for resolving their concerns will be in each particular case. However continued failure to utilise the formal collective measures risks allowing States engaged in toxin and bioregulator weapons development to more easily ignore or dismiss well-founded concerns as being groundless politically motivated attempts to undermine or tarnish the international reputation of the accused States. Once again failure to use the formal CWC and BTWC mechanisms has the additional broad corrosive effect of undermining confidence in the relevant control regime.

These arguments are reinforced by growing concern now in an era of hybrid warfare and extensive social interaction via the internet of the potential for the ever more sophisticated use of disinformation about chemical and biological weapons defence and potential biological and chemical weapons development programmes, in the pursuit of other geopolitical and military purposes. In recent years Russia, supported by China, appears to have conducted active and concerted biological weapons disinformation campaigns. Previously, these apparent disinformation campaigns have focused on concerns around US biodefence as well as US support for similar activities taking place in former Soviet Union States, notably in Georgia. Recently, such Russian apparent disinformation has been given a further dangerous twist following its invasion, on 24 February 2022, of Ukraine. On 11 March 2022, Russia initiated a debate by the UN Security Council, of its allegations that Ukraine "has a network of at least 30 biological laboratories that host extremely dangerous biological experiments, aimed at *enhancing the pathogen properties* of … *lethal diseases with the help of synthetic biology [and that] this work is funded and directly supervised by … the United States*" (emphasis added).[9] The UN High Representative for Disarmament Affairs, Izimu Nakamitsu, commented on the Russian allegations by stating that the "United Nations is not aware of any biological weapons programmes."[10] The Russian allegations were

[9] United Nations Security Council (2022) *Statement by Permanent Representative Vassily Nebenzia at UNSC briefing on biological laboratories in Ukraine*, 11 March 2022.

[10] United Nations Security Council (2022) *High Representative's briefing to the Security Council on Threats to International Peace and Security, Statement by Ms. Izumi Nakamitsu, High Representative for Disarmament Affairs*, 11 March 2022.

forcefully refuted by a number of States during the UNSC meeting[11] and also in an emergency session of UN General Assembly.[12] Ukraine, along with the US and other States that provide support to biological research in Ukraine, has previously been transparent about its activities. They annually declare such activities under the BTWC's confidence-building measures, and they voluntarily share this information publicly. In contrast, Russia has not publicly presented substantive credible evidence to support its allegations. Disinformation campaigns if not actively identified, confronted, and condemned will erode trust among CWC and BTWC States Parties and could seriously degrade the effectiveness of both Conventions and the associated control regimes.

10.3.5 Implications of Ambiguities and Structural Weakness in the BTWC and CWC

The review in Chap. 9 highlighted a range of significant textual ambiguities and limitations in the BTWC and CWC of direct relevance to the regulation of toxins and bioregulators. For the BTWC, whilst Article 1 clearly ensures that toxins (and bioregulators) are covered under the scope of the Convention and their weaponisation prohibited, the negotiators failed to define toxins and clarify the range of substances covered by this term. Similarly, whilst States Parties subsequently collectively clarified that the BTWC coverage extended to "all…artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of their origin and method of production" and consequently included synthetic analogues of toxins and bioregulators, the precise nature and range of the chemicals covered has not been defined and is left to individual State interpretation. Similarly, whilst the CWC definition of "toxic chemicals" clearly encompasses toxins, bioregulators and their synthetic analogues, and their development, acquisition and use as weapons is prohibited; with the exception of ricin and saxitoxin, the negotiators failed

[11] United Nations Security Council 8991ST Meeting (AM), Meeting coverage (2022) United Nations Not Aware of Any Biological Weapons Programmes, Disarmament Chief Affirms as Security Council Meets to Address Related Concerns in Ukraine, SC/14827, 11 March.

[12] United Nations (2022) *11th Emergency Special Session of the UN General Assembly on Ukraine*, Convened by S/RES/2623 (2022).

to incorporate toxins and bioregulators into the Convention's standard monitoring and verification mechanisms.

Furthermore, for both Conventions, there was a similar lack of clarity as to whether and if so which toxins, bioregulators, and synthetic analogues, beyond RCAs, could be developed as law enforcement weapons; to the situations in which such weapons could legitimately be employed, and under what constraints; and finally how legitimate law enforcement use could be demarcated from armed conflict. These ambiguities were exacerbated by failures of definition or insufficient guidance relating to key terms, notably "law enforcement" and "domestic riot control purposes" in the CWC; and in the BTWC "hostile purposes", and "prophylactic, protection and other purposes". Further ambiguity surrounds the extent to which relevant research that may be associated with toxin and bioregulator weapons development can be regulated under both Conventions to ensure it is not actually employed for developing such weapons intended for armed conflict, or other malign purposes.

Perhaps for both the BTWC and the CWC, a degree of 'constructive ambiguity' was useful and even indispensable in developing the respective Convention text that all negotiating States could sign up to, given the opposing positions of some States on certain issues during both negotiations. Such textual in-exactitude is by no means unusual in international agreements. Where such ambiguity exists in international agreements, States have recourse to legal tools and guidelines to aid them in their interpretations of the text, most importantly the UN Vienna Convention on the Law of Treaties.[13] However, even utilising such interpretive tools, the absence of definitional clarity and the consequent textual ambiguity that can result if left unresolved over a lengthy period of time can become dangerous, leading to differing interpretations of the BTWC and the CWC by States Parties. This, in turn, could potentially lead to breaches of the relevant Convention by some States Parties and also to an erosion of the stability and key prohibitions of the regime as a whole.

These concerns are illustrated in our country case studies. For example, did Soviet scientists and officials believe, as reported by whistleblowers, that research and development of bioregulator weapons was not prohibited under the BTWC? Does the current Russian administration believe that "genetic weapons" are a legitimate line of research permitted by the

[13] United Nations (1969) *Vienna Convention on the Law of Treaties*. Vienna, 23 May; 1155 UN Treaty Series (UNTS) 331.

BTWC and CWC? Did former US administrations believe that constructing biological weapons as part of threat assessments was a legitimate aspect of biodefence not prohibited under the BTWC? Do US military officials believe that capsaicinoids are not covered by the BTWC and that malodorants should not be considered as either "toxic chemicals" or RCAs under the CWC? What exactly did Indian defence scientists mean when they described their work on toxins derived from plants as being exploited for "the development of novel multisystem targeted agents for self-defence" and how can such activities be consistent with the CWC and BTWC? Whilst these divergent, and in certain cases clearly incorrect, interpretations of the BTWC and/or CWC are extremely troubling in themselves, concern is exacerbated by the failure of the relevant control regimes to acknowledge or address them. An additional, highly contested, area, illustrated particularly in the Chinese, Russian, and US case studies and now only partially addressed, was whether CNS-acting chemicals, including toxins, bioregulators, and their synthetic analogues, could be utilised for law enforcement and if so for what purposes and under what constraints. Similarly, the regulation of riot control agents (including those of a biological origin) and associated means of delivery was not sufficiently clarified in the Conventions and is an area where divergent State practice is apparent with potentially damaging consequences.

The potentially deleterious consequences following from the ambiguities in the BTWC and the CWC texts have been played out through, and further exacerbated by, the limitations in the structure, working practices and culture of the attendant control regimes established to facilitate implementation of the two Conventions. With regard to the CWC, there has been a long-standing limited ability of the OPCW to address certain important or pressing issues, even if delays in action could seriously weaken the effectiveness of the Convention. Factors contributing to this situation have included the organisation's culture of decision-making by consensus and the consequent avoidance of difficult or controversial issues, the wide disparity in resources, and scientific and technical expertise available to State Party delegations and national authorities, the limitations on the autonomy of the OPCW's Technical Secretariat including its inability to formally receive and act on open-source information, and the limited transparency and accountability of the OPCW to civil society. Recently however, the OPCW has increasingly found innovative ways to work around organisational obstacles and has been attempting to address some of its systemic failings. Notable advances have included its work to

facilitate and verify Syrian destruction of declared CW facilities and stockpiles, establishment of a mechanism to identify chemical weapons perpetrators, and adoption of the "understanding" prohibiting aerosolised use of CNS-acting chemicals in law enforcement. The situation is far bleaker for the BTWC control regime which faces important long-standing and deeper systemic weaknesses that severely limit the value of the BTWC as a tool to prevent and address the development of toxin and bioregulator weapons. These include the current lack of effective transparency, verification, and compliance mechanisms; inadequate monitoring and review of advances in relevant science and technology; and also, the absence of a sufficiently resourced international organisation empowered to coordinate such activities and to facilitate effective implementation by States Parties.

10.3.6 Issues Related to the Response of the Scientific Community to Chemical and Biological Security

Our country case studies revealed numerous issues related to the response of scientists and the scientific community to the problem of dealing with chemical and biological security in the twenty-first century. We have divided these issues into the following four sub-sections.

10.3.6.1 Building a Culture of Responsibility to Prevent Misuse of Chemical and Life Science Research

Individual chemical and life scientists in certain countries have been associated with or actively participated in State-level toxin and bioregulator weapons development programmes. In many cases the precise nature of their involvement was unclear as was their true agency and motivation, and the knowledge they had of the ramifications of their actions and intended purposes behind such programmes. In addition to direct involvement in dedicated weapons programmes, far greater numbers of chemical and life scientists throughout the world appear to be engaged in dual-use research activities which are potentially of concern and the implications of which they are either not sufficiently aware of or not concerned about.

In 2004 the International Committee of the Red Cross (ICRC) issued a statement "Preventing Hostile Use of the Life Sciences", in which it declared: "If measures to prevent the hostile use of advances in the life sciences are to work, a culture of responsibility is necessary among

individual life sciences."[14] According to the ICRC, such a culture of responsibility should apply "whether these scientists are working in industry, academia, health, defense or in related fields such as engineering and information technology", and should encompass the "institutions that employ scientists and fund research in the life sciences." Despite subsequent concerted attempts by national and international chemical and life science associations to nurture awareness of individual scientists and relevant institutional research oversight bodies to the dangers of the misuse of the chemical and life sciences and the consequent responsibility to prevent such misuse, there continues to be widespread ignorance and apathy to such dangers. This has been recognised recently in the 2022 World Health Organization (WHO) draft *Global guidance framework for the responsible use of the life sciences*,[15] which stated that:

> governance and oversight frameworks to manage the risks posed by science and technologies lag behind developments and innovation in the life sciences…. *there is an important lack of awareness of these biorisks and a lack of incentives among practising scientists, technologists and other managers and funders of scientific research and technology development to identify and mitigate such risks.* (Emphasis added)

In addition to action by States, we believe the international scientific community has a duty to greatly enhance its efforts to nurture a culture of responsibility, firstly to sensitise individual scientists and scientific associations to the danger of the malign application of their dual-use research, and secondly to confront the intentional participation of certain life scientists in State biological and chemical weapons development programmes.

10.3.6.2 Strengthening Chemical and Life Science Systems Regulating 'Dual-Use' Research

At the heart of the dilemma regarding the regulation of dual-use research is how and where to strike the balance between allowing scientific progress and open-source disclosure, and ensuring against potential misuse of that

[14] International Committee of the Red Cross (2004) *Preventing Hostile Use of the Life Sciences: From Ethics and Law to Best Practices.* ICRC, Nov 11. Cited on 4 Sep 2016, at https://www.icrc.org/eng/resources/documents/misc/biotechnology-principles-of-practice-111104.htm.

[15] World Health Organization (2022) *Global guidance framework for the responsible use of the life sciences: Mitigating biorisks and governing dual-use research* WHO, Geneva, 22 February, p. 12–13.

knowledge. Much of the discourse amongst the chemical and life science community concerning how best to combat the proliferation and use of biological and chemical weapons has concentrated on regulating the actions of individual life scientists conducting dual-use research of potential concern. Highly influential in this discourse have been the 2004 Fink Report[16] and the 2006 Lemon Report,[17] both produced under the auspices of the National Research Council of the US National Academies. Both reports highlighted the importance of taking a comprehensive approach to analysing dual-use research of potential concern, with the Lemon Report recommending the adoption of "a broadened awareness of threats beyond the classical 'select agents' and other pathogenic organisms and toxins, so as to include, for example, approaches for disrupting host homeostatic and defense systems and for creating synthetic organisms".[18] The broad threat spectrums enunciated by both reports, and particularly that of the Lemon Committee, appeared to capture a wide range of potential toxin and bioregulator agents and associated physiological systems that we have identified as potential targets of weaponisation. As a result of the Fink and Lemon Reports, a range of oversight structures and processes have been established by certain States (notably in Europe and the US) and scientific bodies, academic institutions, funders, and publishers, to review dual-use research of potential concern, in order to assess the risks and benefits of such research and determine whether the proposals needed to be modified or withdrawn.[19]

Unfortunately, the application of such oversight measures appears to have been patchy—with previous independent analysis highlighting the failure of such systems to halt or even identify experiment proposals, scientific papers or research funding applications of potential concern. One potential contributory factory to the limited effectiveness and lack of rigour of their application appears to be the voluntary nature of many of these guidelines and oversight systems, and the attendant lack of consequences for those who do not fully comply with their requirements.

A further concern relates to the limited range of issues being considered by such bodies. The discourse and much of the previous activity

[16] National Research Council (2004) op. cit.

[17] National Research Council (2006) op. cit.

[18] National Research Council (2006) op. cit. p. 216.

[19] For a discussion of such initiatives, see Rappert, B. (2008) The Benefits, Risks, and Threats of Biotechnology, *Science & Public Policy*, **35**(1), 37–43.

appears to have concentrated upon preventing the diffusion of dual-use knowledge, skills, and materials to various non-State actors with malign intent, principally terrorist organisations. Insufficient attention has been given to utilising existing dual-use monitoring mechanisms or adopting additional process to specifically combat the misuse of dual-use expertise in State programmes, even though such dedicated national chemical and biological weapons programmes arguably pose a greater danger to the CWC and BTWC than the more limited activities of non-State actors in this area. Furthermore, as discussed in Sect. 10.3.2, whilst much of the dual-use research of potential concern has shifted from a concentration on potential agents to potential targets, the implications of this shift have not been addressed by research oversight structures.

Nevertheless, there has been some progress in recent years in the development of both a broader conception of the problem and of specific tools and mechanisms to assist scientists and others in dealing with it. This is particularly true in regard to the guidance framework being developed by the World Health Organization. The draft document put out for consultation in early 2022 described a major section of the framework that[20]:

> identifies practical tools and mechanisms for the governance of biorisks, arranged by different groups of stakeholders who have responsibilities in the oversight of biorisks. This section covers both formal and informal governance measures at individual, institutional, national, regional and international levels. It aims to reach different communities associated with the life sciences, from scientists, research institutions, funders and publishers, to those communities working with disciplines that intersect with the life sciences (e.g. chemistry, artificial intelligence and computer science).

The issue that remains is to further develop and particularly achieve implementation of these tools and mechanisms. This brings us again to how the vast scientific community around the world can be made aware and educated enough about chemical and biological security to engage effectively and thus become part of the solution.

10.3.6.3 Codes of Conduct

One approach to building a culture of responsibility has been through the development of a range of non-binding ethical codes, codes of conduct,

[20] World Health Organization (2022) op. cit. p. 13.

and oaths or pledges. The development of codes of conduct became one of the priority areas for BTWC State Party activity from the first BTWC intercessional process in 2003 through to the current intercessional process and the ongoing preparations for the 9th BTWC Review Conference.[21] Building on past activities, China and Pakistan tabled a joint proposal at the 2018 BTWC Meeting of Experts (MX2) for the development of a "model code" for biological scientists. Following further revision, in November 2021, China and Pakistan, and co-sponsor Brazil, submitted the *Tianjin Biosecurity Guidelines* for consideration by the BTWC States Parties at the forthcoming Review Conference.[22] In July 2021, the Guidelines were also endorsed by the Inter-Academy Partnership of National Scientific Academies.

The chemical science community's efforts to develop codes were initially largely focused upon the activities of the International Union of Pure and Applied Chemistry (IUPAC).[23] In a major advance, during the 2014 CWC Conference of States Parties, the German Ambassador introduced his country's proposal for a "Hippocratic Oath" for chemists. Whilst acknowledging the importance of action and responsibility by States, he stated:

> [I]n order to free the world entirely of the danger of chemical weapons, we also have to appeal to the responsibility of individuals…who have the capability to develop and produce chemical weapons. This is the reason why Germany has submitted the proposal of a code [of conduct] for chemical professionals…. Similar to the Hippocratic oath…this concise text could lay the moral basis for the work of chemical professionals.[24]

[21] Whitby, S. Tang, C. Shang, L. and Dando, M. R. (2020) After COVID-19: Time to Agree a Code of Conduct Under the Biological and Toxin Weapons Convention. *Journal of Chemical and Biological Weapons*, Summer, 60–74.

[22] China and Pakistan, Co-sponsored by Brazil, *The Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists*, BWC/MSP/2020/WP.7, 22 November 2021, https://meetings.unoda.org/section/bwc-msp-2020-documents/.

[23] For further discussion of the role of IUPAC and the broader chemical science community in preventing misuse of the chemical sciences see: Crowley, M. *Chemical Control*, Palgrave Macmillan, 2015, pp. 241–257; Crowley, M. Dando, M. R. and Shang, L, *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*, Royal Society of Chemistry, 2018, in particular chapter by Bowman, K, Hay, A and Husbands, J., pp. 517–535.

[24] Germany (2015) *Statement by Ambassador Christoph Israng at the 19th Session of the Conference of the States Parties.* Organisation for the Prohibition of Chemical Weapons, The Hague, 21 January 2015.

Following OPCW endorsement and support of this initiative, the German government funded two workshops held in 2015 to explore these issues and develop an ethical guidelines text.[25] This project was supported and organised under the auspices of the Scientific Advisory Board of the OPCW; and the work was undertaken by an independent international group of scientists from the chemical industry and academia in 24 countries and from all world regions. The resulting *Hague Ethical Guidelines*,[26] echoing previous IUPAC thinking, are a set of non-binding principles that can be used both to support the development of new codes and to review existing codes, in order to ensure they align with the provisions of the CWC.

The proponents of such codes of conduct assert their potential utility in helping to sensitise chemical and life scientists to the dangers of dual-use research, and to reinforce the importance of, and promulgate, ethical "red lines" where the legal prohibitions or normative taboos are already clearly defined and widely accepted. However, the effectiveness of such an approach has been questioned by a range of scholars. One important limitation of the majority of code-based initiatives to date is that the resulting instruments are aspirational and non-binding in nature, with no clearly identified penalties elaborated for those individuals who breach the prohibitions, or mechanisms established to monitor and enforce such prohibitions. Recognising the weaknesses of self-governance initiatives to effect change in this area, some have called for codes of conduct to become binding, with those breaching such codes facing sanction from their peers (or the State). For example, Professor Joseph Rotblat, in a letter to a Pugwash Workshop on Science, Ethics and Society in 2004, stated his belief that: "[P]erhaps the time has come for a binding code of conduct, where only those who abide by the code should be entitled to be practicing scientists, something which applies now to medical practice."[27] We support such a development as a long-term aspiration. In the short term

[25] See: *Report of First Workshop*: https://www.OPCW.org/fileadmin/OPCW/SAB/en/March_2015_Ethical_Codes_Workshop-Report.pdf; *Report of Second Workshop*: https://www.OPCW.org/fileadmin/OPCW/SAB/en/Hague_Ethical_Guidelines_2nd_Workshop_Report.pdf.

[26] OPCW, *The Hague Ethical Guidelines*. Available at https://www.opcw.org/hague-ethical-guidelines.

[27] Rotblat, J. (2004) *Letter to Workshop*. Report of 2nd Pugwash Workshop Science, Ethics and Society, Ajaccio, Corsica, 10th–12th September. Available at http://web.archive.org/web/20130116075455/http://www.pugwash.org/reports/ees/corsica2004/corsica2004.html.

we believe that the community needs to concentrate on ensuring the existing non-binding codes, notably the *Hague Ethical Guidelines*, and those under development, notably the *Tianjin Biosecurity Guidelines*, adequately address the key threats from malign application of the chemical and life sciences.

Though recognising the limitations of voluntary codes, and emphasising that they can never be an effective replacement for adequate binding regulation by the State and/or the scientific community of dual-use research, we believe they clearly have an important complementary role to play in the biorisk management tools and mechanisms advocated by the WHO by fostering awareness and acceptance by individual chemical and life scientists of the responsibilities they bear to prevent the misuse of their research. However, in order to do this, such codes must eventually address ambiguous, controversial, or disputed issues. Unfortunately, a review of existing codes shows that it is precisely in those areas of ambiguity, controversy or dispute, where codes remain silent, or at best provide ambiguous guidance. For example, while supporting the Conventions, neither the *Hague Ethical Guidelines* nor the *Tianjin Biosecurity Guidelines* specifically address the issue of toxin or bioregulator weapons, nor even explicitly state that toxins and bioregulators are covered by the BTWC and CWC. Furthermore, as with dual-use research oversight, whilst numerous codes condemn and seek to prevent the involvement of scientists in development of biological and chemical weapons by non-State actors, it is questionable whether enough energy has been devoted to targeting the more contentious issues of the involvement of life scientists in State-run weapons programmes. Once again neither the *Hague Ethical Guidelines* nor the *Tianjin Biosecurity Guidelines* explicitly address State weapons programmes. We believe that such 'areas of silence' must be urgently addressed in existing and developing codes and attendant promulgation activities—and that participation in State chemical and biological weapons programmes must be explicitly condemned as a clear breach of scientific ethical standards; failure to do so reinforces the existing perception that such issues are somehow 'negotiable' or are not worthy of attention by individual scientists.

10.3.6.4 Chemical and Biological Security Education

Our country case studies have revealed many instances of apparent ignorance or misunderstanding of the requirements of the CWC and BTWC amongst policy-makers, administrators, funders, and scientists. There is

therefore a clear need for more intensive efforts to raise awareness and implement effective education about chemical and biological security amongst the relevant professionals and particularly amongst the scientific communities involved in creating the advances that may be of dual-use concern. Whilst this can be achieved in part through the development and promulgation of comprehensive codes of conduct, to be most effective such efforts must be accompanied by dedicated biological and chemical educational programmes, ideally incorporating imaginative active learning processes.[28] In this regard it is as well to remember the warning given by Australia on the basis of its own experience at the start of the discussion of codes of conduct at BTWC meetings in 2005. In its view at that time[29]:

> Amongst the Australian scientific community, there is a low level of awareness of the risk of misuse of the biological sciences to assist in the development of biological or chemical weapons. Many scientists working in 'dual-use' areas simply do not consider the possibility that their work could inadvertently assist in a biological or chemical weapons programme.

And it continued:

> For most of these researchers, biological weapons issues may seem irrelevant and therefore strong advocacy is required to overcome natural resistance or ignorance. Introducing Codes of Conduct that highlight these issues is an important step in raising awareness. However, it is not enough simply to put such Codes in place. Without effective measures to educate scientists about the existence and importance of such Codes, attitudes and awareness will remain largely unchanged.

Why indeed should scientists be expected to follow a code of conduct if they do not understand the need for the code?

The World Health Organization's 2022 draft *Global guidance framework for the responsible use of the life sciences* is quite clear that biological

[28] Novossiolva, T. A., Dando, M. R. and Martinelli, M. (2021) Enhancing the Utility of Codes of Conduct for Chemical and Biological Security through Active Learning. *ACS Chemical Health and Safety*, Special issue "Safety Policy, and Codes from Around the World", 10.1021/acs.chas.1c00047.

[29] Australia (2005) *Raising Awareness: Approaches and Opportunities for Outreach.* BWC/MSP/2005/MX/WP.29. United Nations, Geneva, 21 June.

security education can be one of the tools and mechanisms that can be effectively used to improve biological security, stating that[30]:

> **Introducing responsible science concepts, including biosafety, biosecurity and dual-use**. Integrating concepts pertinent to conducting responsible research into scientific and medical curricula can enhance awareness of risks to health, safety and security with basic and applied life sciences. Academic and scientific institutions can help by including these concepts in their courses and educational activities. (Original emphasis)

Some BTWC States Parties are well aware of this problem and have financed the development of teaching resources on biological security education and translation of these resources into multiple languages for use overseas.[31] Some Universities have also developed innovative ways of using active learning strategies in teaching biological security to scientists,[32] but correcting the current deficiencies in security education for the many thousands of life scientists around the world will require the long-term application of major resources well beyond anything that has been envisaged to date. It is for this reason that endorsement of the *Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists*[33] by States Parties at the 9th Review Conference, and particularly its Element 6 which stresses the importance of biological security education and training for life and associated scientists, is so critical.

As we have argued, both the *Hague Ethical Guidelines* and the *Tianjin Biosecurity Guidelines* would have been more effective if they had made explicit mention of toxins and bioregulators rather than leaving such coverage implicit. However, no such argument can be made in regard to the WHO *Draft Framework* as the second of its illustrative scenarios[34] is intended to make the point that dual-use concerns range far more widely than just the manipulation of pathogens. This scenario describes a civil

[30] World Health Organisation (2022) op. cit. p. 53.

[31] Whitby, S., Novossiolova, T., Walther, G. and Dando, M. R. (2015) *Preventing Biological Threats: What You Can Do*. University of Bradford, Bradford, December.

[32] Novossiolova, T., Shang, L. and Dando, M. R. (2021) Biological Security Education, Awareness, and Outreach as Essential Elements of Strengthening the Review of Science and Technology under the BTWC. *Journal of Chemical and Biological Weapons*, **Winter**, 36–40.

[33] China and Pakistan (2021) *The Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists*. BWC/MSP/2020/WP.7. United Nations, Geneva, 22 November.

[34] World Health Organisation (2022) op. cit. pp. 92–95.

scientist (Scientist B) working on the structure and function of a bioregulator disruption of which is thought to be the cause of a debilitating illness. Scientist B's work is intended to assist in the development of means of correcting such malfunctions, but he is not aware of the dual-use concerns that could arise from the use of his work to cause the malfunctions until this is brought to his attention at a conference where he is presenting his work. The scenario includes a series of 12 questions such as:

> Has Scientist B received an adequate biosecurity education that would have equipped him to recognize and address dual-use concerns?
>
> Has the institution provided any incentives to its researchers to ensure that an adequate biorisk assessment is carried out before research proceeds?
>
> How can biosecurity checks be institutionally implemented to advise Scientist B of the dangers of malicious misuse of his research and to require him to consider some means of minimizing the dangers?

A series of priority actions that could be taken to improve biorisk management are introduced with that statement that:

> This scenario underlines the need for improved education and training so that scientists, institutions, funders, publishers, and countries are aware of the problem of dual-use and the potential consequences for broader society. Once these stakeholders understand dual-use, they can apply their expertise to helping minimize the risk through their daily jobs, both for individual experiments and more broadly in their field.

These are sentiments that we would endorse given what we have found in the country case studies.

10.3.7 Non-participation and Whistleblowing

Any serious attempt by State or non-State actors to research, develop, manufacture, and stockpile toxin and bioregulator weapons on a significant scale would likely require the involvement of an array of chemical and life scientists, as well as engineers, technicians, and other ancillary workers. Although necessary (whether they be willing or unwilling) participants, they are also potentially capable of 'blowing the whistle' on such weapons programmes through public denunciations, leaking information to journalists, other States, or by formally reporting concerns about potential or

realised breaches of national regulations or violations of international treaties directly to the relevant oversight or regulatory bodies. As highlighted in this book and elsewhere, testimony by life scientists such as Alibek and Popov previously working in the heart of the Soviet Union's vast clandestine biological and toxin weapons programme contributed to finally exposing its illegal activities and paving the way to its eventual termination and dismantlement.

In his 1995 Nobel Peace Prize acceptance speech, Prof Joseph Rotblat stated that: "The purpose of some government or industrial research is sometimes concealed, and misleading information is presented to the public. It should be the duty of scientists to expose such malfeasance." Whilst Rotblat argued that "'Whistleblowing' should become part of the scientist's ethos", he warned "this may bring reprisals; a price to be paid for one's convictions. The price may be very heavy."[35] Although certain States, such as South Africa,[36] the UK,[37] and the US,[38] have legislation safeguarding whistleblowing activities on their statute books, its effectiveness and implementation has been variable. And in the vast majority of States no such protection exists. In fact, in certain States, contemporary potential whistleblowing scientists face extremely punitive national security legislation and practices, including dismissal, harassment, and imprisonment if they dare to speak out.

If it is the duty of individual scientists to make known their concerns about the misuse of scientific research for activities that breach ethical standards or international law, then it is surely the responsibility of the scientific community as a whole to ensure that such whistleblowers are fully protected. This was explicitly recognised by the ICRC in its 2004 statement, which declared that: "[T]hose working in life sciences who voice concern and take responsible action require and deserve political and professional support and protection"[39] Although certain life science

[35] Rotblat, J. 1995) *Nobel Lecture: Remember Your Humanity*. Acceptance and Nobel Lecture, Oslo, 1995, cited 16 Aug 2016. Available at http://www.nobelprize.org/nobel_prizes/peace/laureates/1995/rotblat-lecture.html.

[36] South African *Protected Disclosures Act 26 of 2000*, cited 18 Aug 2016, available at: http://www.justice.gov.za/legislation/acts/2000-026.pdf.

[37] UK Government, *Public Interest Disclosure Act, PIDA*, 1998.

[38] US *Federal Whistleblower Protection Act (5 USC sec. 1201)*, 1989 Jul 9.

[39] International Committee of the Red Cross (2004), *Preventing Hostile Use of the Life Sciences: From Ethics and Law to Best Practices*. ICRC, 11 November. Available at https://www.icrc.org/eng/resources/documents/misc/biotechnology-principles-of-practice-111104.htm.

associations have raised these issues, far more can be done to build "whistleblower" protection and solidarity networks within the life science community. In this regard, it is unfortunate that neither *The Hague Ethical Guidelines* nor the *Tianjin Biosecurity Guidelines* have any element detailing individual responsibility for whistleblowing nor the community's duty to protect such whistleblowers.

10.3.8 Inadequately Regulated and Non-transparent BW and CW Defence and Counter-measures

The country case studies illustrate a wide range of dual-use research and associated activities undertaken by chemical and biological defence establishments into toxins, bioregulators, associated bioregulatory pathways and physiological systems, as well as potential measures to facilitate agent uptake and means of external dissemination. The necessity of such work is recognised and specifically permitted, but only when it is conducted for "protective purposes" under the CWC, or for "prophylactic, protection and other purposes" under the BTWC. Such work requires some level of secrecy with regard to the threats that have been identified by States as being of concern to them, and the responsive measures that are being undertaken. Yet, without adequate assurance that this research and associated work is only for defensive requirements, such as detection and identification of agents for prophylaxis and treatment, and development of protective measures, there are obvious dangers that States could be (or perceived as) attempting to hide weapons development under the guise of defensive research. Whilst reporting and transparency mechanisms have been established within the BTWC and CWC control regimes to build confidence between States that such research and associated activities are only for defensive purposes, there are open questions as to their adequacy and effectiveness. Do they capture the full range of research and associated activities of concern? Do they capture all relevant actors—not just military but also law enforcement, academic and commercial research entities? How can States be confident that activities, many of which are undertaken under classified programmes or in classified facilities, are being fully and truthfully reported? How can States Parties raise and effectively resolve issues of concern?

Furthermore, even such partial and incomplete information exchange—whether through CWC Article X Declarations or BTWC CBMs—is largely restricted to States Parties. Although certain States unilaterally publish

BTWC CBMs, and to a much lesser extent Article X Declarations, much of this information is redacted. Consequently, the ability of civil society to independently monitor chemical and biological defence activities is minimal. There are also wide disparities in the levels of oversight and transparency of chemical and biological defence establishments to their national legislatures. These information deficits limit public accountability and may erode confidence in the benign purposes of the activities conducted in such establishments.

Even from the partial and incomplete information available there are indications that research undertaken in certain State chemical or biological weapons defence establishments may have come near to or actually crossed the line into weapons development, in particular with regard to "threat assessment" activities. As noted earlier, such establishments have a responsibility to do what they can to provide protection and prophylactic measures against likely chemical and biological agents. To an extent, therefore, in addition to responding to current offensive capabilities of enemies, they also have to consider potential future threats. But what constraints should be put on such speculative research? It is difficult enough to think carefully through the potential dual-use implications of defence research of toxins and bioregulators previously explored as weapons, but what happens if military and military-related institutions and scientists start to identify new toxins and bioregulators (or perhaps synthesise new analogues or modify existing toxins and bioregulators) and investigate the mechanisms of action for these potential future threat agents, purportedly in order to work on how to counter them?

In the US, where there has been some, albeit limited, public reporting supplemented by investigative journalism, evidence indicated that previous "threat assessment" projects, including "Bacchus" and "Clear Vision" conducted between 1997 and 2001, skirted if not breached the BTWC. Subsequent disquiet has been voiced over the 2004 establishment of the National Biological Threat Characterization Center (NBTCC) which was reported to have planned capabilities to investigate *inter alia* "Aerosol Dynamics, Novel Delivery of Threat, Novel Packaging, Simulation/Modelling (Epidemiology), Genetic Engineering, Environmental Stability, Bioregulators/Immunomodulators, Genomics/Proteomics/Transcript

[and] Red Teaming [i.e. duplication of threat scenarios]".[40] However, since much of the subsequent NBTCC research has been and continues to be classified, the nature and intention behind such research and associated activities is unknown.

Similarly, the purpose behind the contemporary dual-use research undertaken by India's DRDO and associated bodies into toxins derived from Indian stinging and other poisonous plants is unclear. Is it intended to be a form of "threat assessment" facilitating development of countermeasures to currently non-existent toxin weapons employing "novel biothreat agents" derived from plants that are native to India, or is this research actually intended to facilitate development of new toxin weapons for use by Indian law enforcement or armed forces?

Consideration of the well-known dangers described as the "Security Dilemma", in which efforts to keep up with and to counter possible developments by others merely provokes similar reactions by others, are particularly apposite when examining the implications of "threat assessment" research and associated activities. In certain States it appears that inadequate attention has been paid to ensuring that threat analysis/assessment research does not (and is not incorrectly perceived) as crossing the line to become development of new warfare agents. Unfortunately, it is precisely these contested and innovative research and development activities that States wish to keep secret and are least willing to provide adequate information about, in order to address the concerns of other States and civil society. These kinds of difficulties can be expected to increase because of the convergent nature of the current biotechnology revolution, which is likely to throw up unexpected combinations of advances in linked areas such as nanotechnology and neuroscience.

10.3.9 Complexities of Regulating Dual-Use Research

Dual use is a concept that can be applied to the tangible and intangible features of materials or technology that enable its utilisation for both hostile (e.g. chemical and biological weapons development) and peaceful (e.g. medical) ends with no, or only minor, modifications. In this book we have

[40] Korch, G. (2004) *Leading Edge of Biodefense—The National Biodefense Analysis and Countermeasures Center*. Presentation at the DoD Pest Management Workshop, Naval Air Station, Jacksonville, Florida, Feb. Sponsored by the Armed Forces Pest Management Board Office of the Deputy Under Secretary of Defense (Installations and Environment). Department of Defense, Washington, D.C. February 2–13. Slide 12.

tried to examine, notably through the country case studies, the real-world complexities around identifying relevant chemical and life science dual-use research and then exploring potential indications of whether it is being undertaken for legitimate and necessary benign work on toxins and bioregulators, such as vaccine production, or else is intended for State-run toxin or bioregulator weapons development programmes.

It is important to recognise that neither the BTWC nor CWC prohibits dual-use research, in fact, as discussed in Sect. 10.3.8; both Conventions expressly permit the conduct of such research and associated activities including the production of appropriate quantities of potential warfare agents for "prophylactic, protection and other purposes" under the BTWC and "protective purposes" under the CWC. The open question is how can a State demonstrate that such research being undertaken in its jurisdiction is solely for permitted purposes and is not a preliminary step in a dedicated weapons programme? Conversely how can the international community effectively monitor dual-use research on a global basis, identify specific individual State research programmes of potential concern, conclusively determine whether such research is conducted for malign purposes, and consequently act to prevent such research facilitating and being employed in a weapons programme before weapons development has occurred?

These issues are further complicated by an overlapping secondary conception of dual use, namely a technology that can have either a military or civilian (including law enforcement) function. Both this and the main definition of dual use employed here may well intersect and need to be read together, notably with regard to considerations of the legitimacy under the CWC and BTWC of the research, development, and use of certain toxins and bioregulators (and associated technologies) purportedly intended for law enforcement purposes. These considerations are particularly pertinent when examining dual-use research and associated development of "less lethal" weapons employing toxins or bioregulators that act on the CNS or other core physiological systems, malodorants, riot control agents of biological origin, and associated means of delivery, all purportedly intended solely for law enforcement purposes.

Dual-use chemical and life science research activities would appear to occur along a spectrum—on one extreme comprising a very wide range of research areas that are of only tangential relevance to aspects of toxin and bioregulator weapons development through to a gradually narrowing range of research areas which are essential for developing such weapons. This conceptualisation, in turn, calls for a certain targeting and calibration

in the development of appropriate forms of corresponding regulation, informed by a range of open questions. Are there certain lines of research which should never be permitted as they would greatly enhance existing weapons or would open new weapons capabilities, and have no, or virtually no, legitimate benign application? Are there lines of dual or rather multiple use research that may have vital health benefits, notably vaccine production, but which could also be employed in weaponisation? In what circumstances should such research be permitted, and with what safeguards and reporting requirements? How can the appropriately calibrated regulatory categories be developed, adopted, effectively updated, by whom and under what authority?

To date, discussion of these matters in the life science community has largely been in relation to microbiology and modifications of pathogens. But even here there is still no clear-cut agreement, for example, that Gain-of-Function experiments should not be carried out on very dangerous potentially pandemic pathogens. Yet, as the 2018 European Brain Project "Opinion" on dual use illustrated, potentially dangerous dual-use activities can take place in many other fields of the life sciences[41]—and that is certainly true of work on toxins and bioregulators.

In Chap. 2 we made reference to the view that such advances would lead to a paradigm change in the way chemical and biological weapons may be developed, because instead of finding and modifying natural agents, it will be possible to focus on an increasing number of specific targets within living systems by means of novel agents. Given those circumstances, if an arms race was to break out in this area of research, the advantage would lie with the offence as it could develop many more agents for many more targets than the defence could easily envisage. This is illustrated by the ongoing advances in neuroscience. This danger was clear from a 2014 US National Institute of Health assessment made of the goals of the US Brain Research Project: "In considering these goals and the current state of neuroscience, the working group identified the analysis of the circuits of interacting neurons as being particularly rich in opportunity with potential for revolutionary advances."[42] In short, they thought that

[41] Human Brain Project (2018) *Opinion on 'Responsible dual Use': political, security, intelligence and military research of concern in neuroscience and neurotechnology*. Danish Board of Technology Foundation, Copenhagen, Denmark.

[42] Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Working Group (2014) *Report to the Advisory Committee to the Director, NIH: Brain 2025: A Scientific Vision*. National Institutes of Health, Washington, D.C., June. p. 5.

there were enormous opportunities for understanding the neuronal circuits that underlie our various behaviours and thus of being able to modify such circuits and behaviours for good. We would argue that account should also be taken of the risks that such "revolutionary advances" could instead be utilised for malign purposes. As we pointed out in our review of Chinese research, this growing understanding of the brain does not just relate to simple behaviours such as sedation, but also, as work on Non-Human Primates advances, to our higher order behaviours. The concerns about potential malign application of large-scale cutting-edge neuroscience programmes, exemplified in particular by the Chinese National Brain Project, are deepened when funding and control for a significant part of such research is in the hands of military-related organisations.

Indeed, the concerns over the Chinese National Brain Project highlight another complexity surrounding dual use—in addition to determining the relevance of a particular strand of research to toxin or bioregulator weapons development, is the requirement for determining the actual intention with which such research is being conducted by specific researchers, whether in relevant military or civil research institutes, at that particular moment. The determination of intent is a notoriously difficult problem, complicated by issues of accountability, integrity, and transparency in the particular research institute as well as the relevant State's respect for, and ability to fulfil, its obligations under the BTWC and CWC. The risks of failing to identify and halt dual-use research and associated activities intended for toxin and bioregulator weapons development must be balanced by the needs to protect the researchers or research establishments conducting perhaps very similar dual-use research but with benign intent. As well as the unjust potential damage to individual researcher and research establishment reputations, and concomitant loss of funding opportunities, research into contested but important dual-use areas with benefits to humanity could be needlessly restricted or closed down. Development of standardised prior vetting and subsequent monitoring methodologies, in part based upon objective and transparent criteria may help to identify potential research projects, trajectories, and establishments of potential concern, that would merit closer investigation by the relevant oversight bodies. Undoubtedly, such measures would need to be supplemented by appropriate levels of national and international reporting and transparency measures for current and prospective life science dual-use research projects.

10.3.10 The Regulatory Gap Between the CWC and the BTWC

The BTWC and the CWC were designed by their negotiators, with the inclusion of a General Purpose Criterion (GPC), to be comprehensive and effectively open-ended in scope. They are both intended to cover and regulate naturally occurring and synthetic toxins and bioregulators. Furthermore, both Conventions prohibit the development, production, stockpiling, acquisition, stockpiling, and use of toxin and bioregulators other than for "prophylactic, protective or other peaceful purposes" in the case of the BTWC[43] and for "purposes not prohibited" in the case of the CWC.[44]

However, both the BTWC and the CWC suffer from significant textual ambiguities and limitations affecting their ability to regulate toxins and bioregulators effectively in practice, that have not been collectively addressed by the States Parties. For the BTWC these include failing to define toxins and clarify the range of substances covered by this term; determine whether toxin and bioregulator weapons can be developed and employed for use in law enforcement, and if so, what types of agent could be used, in what circumstances and under what constraints; and clarify how research is constrained under the Convention to ensure it does not facilitate or is not employed in the development of toxin and bioregulator weapons. Although the CWC's scope of "toxic chemical" coverage includes toxins, bioregulators, and synthetic analogues, in practice it lists only two toxins and no bioregulators in its Schedules of chemicals that require specific regulation and are subject to routine verification measures. The application of the Convention in certain relevant areas is contested including the appropriate regulation of dual-use research for "protective purposes", and the legitimacy of research, development, and use of law enforcement CNS-acting weapons, despite the welcome Twenty-Sixth Conference of the CWC States Parties (CSP-26) Decision banning aerosolised use of CNS-acting chemicals in law enforcement. The application of the Convention in other relevant areas, notably to malodorants and

[43] The BTWC prohibition on use of biological and toxin weapons has been established by "Extended Understandings" of BTWC Review Conferences and derives from the Geneva Protocol.

[44] The CWC exemption for the development of "toxic chemicals" for "purposes not prohibited" maintains only as long as "the types and quantities" are consistent with such purposes.

wide area RCA means of delivery, has not been formally raised by States Parties in any OPCW policy making organ.

These systemic failings have been further exacerbated by divergent State interpretation and implementation of the Conventions including with regard to research and possible development of toxin and bioregulator weapons, which again have not been adequately collectively addressed by the States Parties. Consequently, an apparent overlap of the BTWC and CWC regimes' scope with regard to toxins and bioregulators, in practice currently masks a regulatory gap, with neither Convention being effectively implemented so as to ensure these substances are not developed as weapons.

However, comparing both Conventions, it is evident that despite its limitations, the CWC does contain a range of existing mechanisms that could be strengthened and effectively applied to regulate toxins and bioregulators, if States Parties were willing. It also benefits from the existence of a 500-strong staffed Technical Secretariat to oversee and facilitate State implementation of the Convention. In contrast, there are important longstanding and systemic weaknesses that severely limit the value of the BTWC as a tool to prevent and address the development of toxin and bioregulator weapons. These include the current lack of effective transparency, verification, and compliance mechanisms; inadequate monitoring and review of advances in relevant science and technology; and the absence of a sufficiently resourced international organisation empowered to coordinate such activities and to facilitate effective implementation by States Parties. It therefore appears that the CWC and the associated OPCW provide the best opportunities in the short to medium term for regulating bioregulator and toxin dual-use research and associated activities of concern to ensure that they are not, and are not perceived to be, employed for malign purposes. Consequently, whilst exploring measures to strengthen the BTWC and to enhance cooperation and collaboration between the two control regimes, our Recommendations will focus on the CWC and OPCW.

10.4 Recommendations

It is evident from our findings that aspects of contemporary chemical and life science research into toxins, bioregulators, and bioregulatory pathways raise dual-use concerns. Unfortunately, the most relevant international instruments (i.e. the BTWC and the CWC) have structural

ambiguities and limitations with regard to toxins and bioregulators, exacerbated by divergent interpretations and patchy implementation by their States Parties. Consequently, the existing measures in place to monitor and regulate such research, address activities of potential concern and prevent their utilisation in State toxin and bioregulator development programmes are proving inadequate. Our investigations suggest that individual States, the relevant BTWC and CWC institutional structures, and the international chemical and life science communities can play important roles in addressing these issues.

10.4.1 Individual BTWC and CWC States Parties

10.4.1.1 Fulfil Existing Reporting Obligations and Introduce Additional Transparency Mechanisms

As an immediate first step, it would be beneficial if those States where either past or contemporary activities apparently related to the development or utilisation of toxin and bioregulator weapons have been reported, provide clarification as to the nature and purpose of such activities through an appropriate mechanism of the BTWC and/or CWC control regime. It would build confidence, and help to remove misperceptions, if such clarifications were public and on-the-record, for example through National Statements to the CWC Conference of States Parties, BTWC Meetings of States Parties, or relevant Review Conferences.

CWC States conducting research into toxins and bioregulators for "protective purposes" are required, under Article X (4) of the CWC, to report such activities to the OPCW Technical Secretariat in their annual Article X Declarations. Such declarations should provide sufficient information for the States Parties and the OPCW as a whole, to make informed assessments of the purpose and nature of relevant research and associated activities. To build confidence and help to remove misperceptions, the OPCW should review the information currently provided by Member States in their declarations and consider revision of the current Article X (4) Declaration template form to elicit further information specifically with regard to research related to non-Scheduled agents including toxins and bioregulators. To promote transparency and accountability to civil society, individual States should consider making their annual Article X Declarations publicly available. In addition, to further mitigate misperceptions and increase confidence at the national level, CWC States Parties

should introduce appropriate independent national oversight systems reporting regularly to the legislature.

For the BTWC, during recent intersessional (MX3) meetings on National Implementation, States Parties have given particular attention to facilitating increased levels of submission and fuller responses by States in their annual CBM reports.[45] Although recent efforts to increase CBM submission rates have gradually borne fruit and should be continued, levels are still unacceptably low, with only 92 out of 183 States Parties submitting their annual CBM reports in 2021.[46] CBM Form A1 on laboratories that meet very high biosafety standards, Form A2 on national biological defence research and development programmes, and Form C on the encouragement of publication of results of research directly related to the Convention could capture some of the contemporary research of potential concern on toxins and bioregulators, whilst Form F on past activities in offensive and/or defensive biological research and development programmes is also of relevance. However, it appears from our case studies that the information provided by certain States through the present voluntary CBM report system has not been sufficient to prevent suspicions arising of malign application in rapidly advancing fields of research such as on toxins and bioregulators. This indicates that an overhaul of the CBM system is required, perhaps incorporating some form of peer-review process to assess and improve the quality of information provided by States in their annual reports. Such improvements in State information sharing should be coupled with far greater transparency and accountability to civil society, and an expectation that all States submitting CBM reports will make unredacted versions publicly available.

However, a fundamental obstacle to strengthening BTWC oversight remains, namely how to establish effective verification measures. The stalemate that has blocked progress over the past 20 years will continue as long as those who argue that only incremental modular change can be made and those who say that an overall solution in a legally binding instrument (i.e. Verification Protocol) is the only way forward are unwilling to compromise. We believe that in order to make the necessary

[45] Japan (2018) *Step-by-Step Approach to CBM Participation*. BWC/MSP/2018/MX3/WP. 6. United Nations, Geneva, 6 August; Japan et al. (2019) Revised proposals to Enhance Confidence-Building Measures Participation. BWC/MSP/2019/WP.2. United Nations, Geneva, 20 July.

[46] UN BWC ISU, Submissions made by States Parties by year: 2021, https://bwc-ecbm.unog.ch/?field_form_year_tid=557.

strengthening of the BTWC required after the pandemic, both courses of action should be followed. Some immediately applicable modular steps should be agreed at the 9th Review Conference, and the longer-term health of the Convention should be pursued by a genuine attempt to find a way to an overall solution, including legally binding verification measures, within which the modular elements such as the CBMs can eventually fit.

10.4.1.2 Utilise Existing Consultation, Investigation, and Fact-Finding Mechanisms

If a State has information indicating that another State has been conducting research and development of toxin and bioregulator weapons, they should bring this information to the attention of the BTWC and/or CWC States Parties through the appropriate institutional mechanisms depending on whether the concerned States are party to the relevant Convention. If the concerned States are party to both the BTWC and CWC, both institutional mechanisms should be informed. States should avoid making allegations without being prepared to fully substantiate them and allow them to be investigated through the relevant institutional mechanisms. Where appropriate such information should be placed in the public domain.

CWC States Parties have an array of mechanisms available to them through the OPCW, for highlighting and resolving these concerns. If such concerns can be resolved via bilateral consultation, and the relevant States Parties agree, in order to dispel misperceptions, the results of such consultations should be made known to all States Parties and, if appropriate, to the wider public. If bilateral consultations with the relevant States Parties do not prove fruitful, concerned States Parties should consider initiating, under Article IX of the CWC, the formal multilateral consultation, investigation and fact-finding mechanisms which include on-site challenge inspections of any facility or location in the territory or in any other place under the jurisdiction or control of the State Party of potential concern.

Although the BTWC formal mechanisms are more limited, States Parties with toxin and bioregulator concerns should consider employing the problem-solving provisions under Article V. If initial bilateral consultations prove ineffective, States can initiate the Article V provisions for multilateral engagement, that is, a formal BTWC consultative meeting, as employed by Cuba in 1997. Where States have evidence of BTWC

non-compliance that has not been resolved they should employ the Article VI provision to bring a complaint to the United Nations Security Council which may request the UN Secretary General to investigate the issue.

10.4.1.3 State Application of Other Relevant International Law

Whilst the BTWC, CWC, Geneva Protocol, and related customary international law comprise the *lex specialis* prohibiting States from developing, acquiring, stockpiling, and using biological and chemical (including toxin) weapons, there is additional relevant international law further constraining the weaponisation of such substances. Consequently, States should give full and careful consideration to the application of such international law: firstly because of the direct obligations that arise from such law which may either prohibit or severely restrict development, stockpiling, transfer, or use of weapons employing toxins and bioregulators, and secondly because relevant international law should inform the implementation of those areas of the BTWC and CWC where treaty language is ambiguous and interpretation is currently contested. International humanitarian law (IHL) and international human rights law (IHRL) are of particular relevance, given the potential broadening of malign application of the chemical and life sciences, including and beyond the battlefield, to encompass novel forms of manipulation, punishment, and repression of individuals, groups, or entire populations.

International Humanitarian Law[47]

In terms of armed conflict, States should explore application of existing constraints imposed by international humanitarian law instruments (principally the Four Geneva Conventions and Additional Protocols) and customary IHL, and the consequent implications for State actions in this area. Indeed, the use of toxin and bioregulator weapons in armed conflict would potentially breach relevant IHL prohibitions (such as those forbidding superfluous injury or unnecessary suffering, indiscriminate weapons, and deliberate attacks on civilians). IHL also provides protection to prisoners of war or others considered *hors de combat*, for example, prohibiting

[47] For further discussion of related issues see: Crowley, M. (2018) International legal constraints upon the weaponization of toxic chemicals, pp. 146–192 in: Crowley, M. et al. (Eds) Preventing Chemical Weapons: *Arms Control and Disarmament as the Sciences Converge*. Royal Society of Chemistry; Crowley, M. (2016) *Chemical Control Regulation of incapacitating chemical agent weapons, riot control agents and their means of delivery*, Palgrave Macmillan, pp. 152–165.

the use of toxic chemicals (including toxins and bioregulators) against them in forced interrogations, torture or human experimentation. In addition, further potential constraint on toxin and bioregulator weapons development and use would derive from States' obligations under Article 36 of Additional Protocol 1 to conduct reviews of any new weapon (including toxin and bioregulator weapons) developed or acquired, so as to determine its compatibility with the principles of IHL.

International Human Rights Law[48]

Because international human rights law covers the full use of force spectrum from law enforcement activities through to armed conflict, including 'grey areas' such as counter-terrorist, counter-insurgency and military operations outside of armed conflict, States should explore its application to any potential use of weapons employing toxic chemicals (including toxins and bioregulators) in such circumstances. While several human rights norms may be applicable to the regulation of such weapons or to other malign employment of such substances, the rights to life; and to freedom from torture and other cruel, inhuman or degrading treatment or punishment; together with attendant obligations on the restraint of force, are the most relevant.[49] An important aspect of human rights law is that there are a number of international and regional mechanisms to monitor adherence to relevant treaties. In addition, certain treaties provide for the possibility of individual petition which can result in legally binding judgements for those States party to the relevant instrument (as was seen in the European Court of Human Rights rulings on the use of a CNS-weapon by Russia). However, it must be recognised that these monitoring and enforcement mechanisms have limited preventative value (though they may have some deterrent effect), as they would only be initiated after a potential misuse of such weapons has occurred. Furthermore, there are currently no internationally accepted procedures, under IHRL, for evaluating new weapons, or for monitoring their subsequent use at a national level.

[48] For further discussion of related issues see: Crowley, M. (2018) International legal constraints upon the weaponization of toxic chemicals, pp. 146–192 in: Crowley, M. et al (Eds) *Preventing Chemical Weapons*: Arms Control and Disarmament as the Sciences Converge. Royal Society of Chemistry; Crowley, M. (2016) *Chemical Control Regulation of incapacitating chemical agent weapons, riot control agents and their means of delivery*, Palgrave Macmillan, pp. 166–189.

[49] Other potentially applicable rights include those to liberty and security; to freedom of opinion, association and assembly; to human dignity; and to health.

10.4.2 Collective Measures Under the CWC and BTWC Control Regimes

10.4.2.1 Ensure the Effective Application of the General Purpose Criterion

During BTWC and CWC Review Conferences, the relevant States Parties should reaffirm the importance of the General Purpose Criterion (GPC) contained in both Conventions' Article 1, as a vital safeguard ensuring both Conventions' comprehensive scope and future-proofed prohibition of respectively biological and toxin weapons, and chemical weapons. This reaffirmation would effectively re-enunciate that both Conventions cover toxins and bioregulators within their scope. Subsequently, the OPCW and BTWC Implementation Support Unit (ISU)/States Parties should ensure this reaffirmation is translated into effective and uniform implementation of the GPC by all States Parties at the national level. This is particularly important, given long-standing concerns over divergent interpretation and inconsistent implementation of the GPC amongst States Parties with the consequent dangers of the weakening of their prohibition.

To facilitate effective and consistent implementation of the CWC, the OPCW should establish a consultative process (e.g. an Open Ended Working Group) to develop guidelines on how the "types and quantities" principle of the GPC should be applied in practice. Development of such guidelines should be informed by technical input from the Technical Secretariat and the Scientific Advisory Board. The consultative process should explore the specific challenges to the GPC arising from contested interpretation amongst States Parties as to the range of toxic chemicals (notably including toxins and bioregulators) and associated delivery mechanisms that could be legitimately employed for law enforcement, and the nature of what constitutes legitimate use. In its deliberations the consultative process should consider existing obligations under relevant international law, notably IHRL, and their bearing on the CWC in this area. It should specifically address the following issues:

Riot control agents: Clarify the nature and scope of activities consistent with "law enforcement including domestic riot control". Building upon the previous work of the SAB identifying chemicals (including those of

biological origin) that fulfil the definition of RCA,[50] guidance should be developed as to the quantities of identified riot control agents that can legitimately be employed in law enforcement. Such guidance should acknowledge relevant obligations under IHRL, to ensure such RCA employment is proportionate, necessary, and does not endanger life or health.

Malodorants: Examine the properties of those malodorants previously and currently explored as weapons by States and clarify whether such substances fulfil the definition of "RCAs" and/or "toxic chemicals" under the CWC. Provide guidance as to whether such substances can be legitimately employed in law enforcement and if so under what circumstances and with what constraints.

Delivery mechanisms: Determine which delivery and dispersal mechanisms purportedly intended for riot control agents (including those of biological origin and their synthetic analogues) and potentially applicable to other toxic chemicals are inappropriate for law enforcement purposes and would consequently breach Article II.1 of the Convention. Such prohibited means of delivery should at a minimum include artillery shells, aerial bombs, mortar shells, cluster munitions, and other mechanisms that are indiscriminate or deliver quantities of RCAs likely to cause death or serious injury to those targeted. Provide guidance as to which RCA means of delivery can be legitimately employed in law enforcement and if so under what circumstances and with what constraints.

CNS-acting chemical agent weapons: Following the adoption of the "understanding" by CSP-26, the aerosolised use of CNS-acting chemical agents for law enforcement purposes is effectively prohibited. Further guidance is, however, needed to define "CNS-acting chemicals" and the range of chemicals that would be covered by the "understanding". Additional guidance is also required in order to ensure that any existing or future law enforcement weapons that use toxic chemicals (including toxins and bioregulators) that act on other core human physiological processes

[50] OPCW Technical Secretariat, Office of Strategy and Policy (2014), *Note by the Technical Secretariat, Declaration of riot control agents: advice from the Scientific Advisory Board*, S/1177/2014. OPCW, The Hague. See also Scientific Advisory Board (2017) *Response to the Director-General's Request to the Scientific Advisory Board to consider which riot control agents are subject to declaration under the Chemical Weapons Convention*. SAB-25/WP.1. OPCW, The Hague, 27 March.

beyond the CNS are also prohibited. Guidance should further clarify that not only aerosolised but all weaponised use of such toxic chemicals for law enforcement purposes, no matter how they could be delivered, should be prohibited.

At a minimum the BTWC States Parties should at the forthcoming Review Conference adopt an Extended Understanding incorporating a clear reaffirmation of the importance and comprehensive nature and scope of the BTWC's GPC. In addition, the BTWC States Parties could also consider establishing an appropriate process to examine and collectively define the terms "toxins" and "other biological agents" as employed under the Convention and to clarify the nature and range of substances covered by these terms. This process could also examine and seek to clarify application of the BTWC with regard to those riot control agents, malodorants and incapacitating chemical agents of biological origin and their synthetic analogues. Whilst we recognise that the time may not be ripe for the forthcoming BTWC Review Conference to adopt formal measures to examine these issues, we believe that informal consultations and side meetings could now be initiated by individual BTWC States Parties, with a view to subsequent introduction of the topic into future BTWC MXs and MSPs, when appropriate.

10.4.2.2 Strengthening Science and Technology Monitoring and Review

Advances in science and technology can significantly alter the implementation environment of the BTWC and the CWC, and they may even affect the scope of their prohibitions. Consequently, it is crucial that both the OPCW and ISU/BTWC States Parties conduct in-depth, systematic, and holistic analysis of relevant science and technology advances, including those related to toxins and bioregulators, as part of the activities of the five-yearly Review Conferences. To facilitate such activity it is essential that independent technical advice is provided to the States Parties concerning developments in relevant science and technology and their potential impacts upon the operation of the Conventions. Such technical expertise is provided to CWC States Parties through the Scientific Advisory Board (SAB) and the OPCW Technical Secretariat with the long-standing cooperation of the International Union of Pure and Applied Chemistry (IUPAC).

CWC States Parties should ensure more frequent and considered review by the OPCW of relevant advances in converging chemical and life sciences and technology, and the implications for the Convention. In

addition to the broad-scope review currently undertaken every five years in preparation for the Review Conference, the SAB and the Technical Secretariat should consider further development of its current analysis of specific issues or technologies of potential concern to specifically include toxins and bioregulators. In this regard we very much welcome the establishment, in January 2021, of the SAB Temporary Working Group on the analysis of biotoxins.

In addition, the CWC States Parties should further enhance the Technical Secretariat's in-house capability to monitor advances in science and technology of potential concern to the Organisation; suitable mechanisms should also be established to allow the Technical Secretariat to bring relevant concerns *proactively* to the attention of the Executive Council and the States Parties, in a timely manner, and not be restricted to responding to their requests.

To date for the BTWC there is no body, comparable to the OPCW's SAB, tasked with providing independent expert scientific advice to the States Parties. In recent years, BTWC States Parties have discussed establishing a dedicated mechanism to review and assess science and technology of relevance to implementation of the BTWC. As with the OPCW SAB, the proposed mechanism could, for example, regularly provide States Parties with overview reports of relevant science and technology (S&T) developments to inform and facilitate their discussions at Meetings of Experts (MXs), Meetings of States Parties (MSPs), and Review Conferences. This option has achieved broad consensus on the need for the mechanism's membership to be geographically diverse, incorporate a wide range of scientific expertise, and be independent of political influence, but agreement is still to be reached on the mechanism's structure. Regardless of the eventual structure, we believe for it to be effective the S&T review mechanism must be supported with adequate financial, technical, and human resources, which should include the establishment of a dedicated S&T staff post in the ISU with responsibilities for servicing this mechanism. Following agreement at the Review Conference, it is important that States Parties move quickly to establish this mechanism, recruit staff, agree rules of procedure, and develop a schedule which details issue areas of particular initial concern. We would argue that the implications of rapid advances in toxin and bioregulator research should be an immediate area of concern. More broadly, States Parties should also consider how this mechanism could cooperate and collaborate with relevant structures in the OPCW, notably the SAB, on areas of mutual concern notably toxins and bioregulators, as discussed in the next section.

10.4.2.3 Addressing the BTWC/CWC Regulator Gap

As the sciences of chemistry and biology converge with information technology and mathematical modelling, the historical accident of there being two different international instruments dealing with what is in effect one spectrum of potential agents becomes increasingly difficult to manage. This problem is exacerbated by the different locations and vast differences in size and capabilities between the two international organisations responsible for the CWC and the BTWC. States Parties to both Conventions should address how the two control regimes and institutional organisations can cooperate more effectively, particularly with regard to regulating the mid-spectrum agents, that is, toxins and bioregulators that fall under the scope of both Conventions.

Some engagement has already taken place at the technical scientific level, facilitated by the OPCW SAB and Technical Secretariat, notably following the study and 2014 report of the SAB TWG on convergence of chemistry and biology.[51] This has included regular side events held in the margins of BTWC meetings and scientific conferences, which have provided fora for the OPCW Technical Secretariat and the SAB to interact with experts from the BTWC. The SAB Temporary Working Group on convergence itself provided a unique international vehicle for interaction of experts from both the BTWC and CWC and associated scientific communities. The OPCW should consider establishing a forum similar to this TWG, possibly as a temporary working group or better a standing arrangement under the SAB. Such a forum could facilitate greater synergies in areas of existing parallel activities such as monitoring and assessment of developments in chemical and life sciences of relevance to both Conventions, and outreach and promulgation to the chemical and life science communities.

At the institutional level, the OPCW Technical Secretariat and the BTWC Implementation Support Unit should examine the effectiveness of existing measures to facilitate information exchange, cooperation, and collaboration over areas of joint concern, notably regulation of toxins and bioregulators, and how these can be strengthened to respond to the implications of the growing convergence of the chemical and life sciences. The OPCW TS and the BTWC ISU should explore the utility of developing a Relationship Agreement or Memorandum of Understanding (MOU) to

[51] OPCW, (2014) *Convergence of Chemistry and Biology Report of the Scientific Advisory Board's Temporary Working Group*, SAB/REP/1/14, 27 June.

formalise and facilitate increased cooperation and collaboration between the two Organisations. The OPCW currently has such a Relationship Agreement with the United Nations, and MOUs in place with other international and regional bodies including the UN Office for Disarmament Affairs, World Customs Organisation, and the African Union Commission and also IUPAC, but not, to date, with the BTWC ISU. Such a Relationship Agreement or MOU could establish how the two institutions cooperate in cases where, for example a State has been formally accused, or itself declared possession, of toxin and bioregulator weapons stockpiles or production facilities; or clarify how both institutions can collaboratively respond and facilitate assistance provision to a State that has been attacked by toxin or bioregulator weapons.

10.4.2.4 Strengthening Routine OPCW Monitoring and Verification Measures Applicable to Toxins and Bioregulators

For the OPCW, the existing Schedules of chemicals, which remain important triggers of routine industry monitoring and verification measures for traditional chemical warfare agents, include only two toxins (ricin and saxitoxin under Schedule 1) and currently no bioregulators. However, as a result of advances in and the convergence of the chemical and life sciences, new potential chemical warfare agent types involving intermediates and products not listed on any of the Schedules (including toxins and bioregulators) may become increasingly relevant. Consequently, the industry monitoring and verification regime, as well as the analytical methods and databases available for challenge inspection and investigation of alleged use, needs to be reviewed and adapted to these new technological and chemical realities. These issues have in part been recognised by the OPCW, with the Director General in January 2021 establishing a SAB Temporary Working Group on the analysis of biotoxins which will explore "classes of biological toxins [that] are most likely to be relevant in investigations of alleged use"[52] and "other relevant compounds of biological origin that should also be considered based on their potential for misuse or technological change associated with them".[53]

With regard to strengthening the routine industry and verification apparatus, consideration could be given to updating the Schedules themselves, for example, by adding further toxins that have been or may be

[52] OPCW (2021) SAB, 5(b).
[53] OPCW (2021) SAB, 5(c).

utilised in weapons programmes such as SEB and botulinum toxin; and also providing indicators of the new types of potential chemical agents (and their precursors) of concern, notably bioregulators such as Substance P. Although symbolically important, the practical effects of such additions are uncertain, particularly for bioregulators, given the large number of bioactive peptides being synthesised; furthermore the amounts of such bioregulators being produced may be too low to trigger the CWC's industry verification system. A further concern is that adding bioregulators to Schedule 1 would limit the amounts that could be produced for benign and potentially vital medical purposes. An alternative, proposed by Tucker,[54] would be to modify the provisions in the CWC Verification Annex that cover other chemical production facilities (OCPFs) which produce by synthesis more than 200 metric tons per year of organic chemicals not listed by name in the CWC. Tucker posited developing a subcategory for those facilities that manufacture peptides with a production threshold of between 50 and 100 kilograms per year, thereby capturing OCPFs that could support State-level bioregulator weapons production.[55] We believe that both options should be examined by the CWC States Parties. Such changes can be undertaken through an expedited amendment process under Article XV of the Convention, and with regard to Schedule changes, were employed for the first time in November 2019 to add several chemicals associated with the Novichok family of nerve agents and carbamates to Schedule 1.

10.4.3 Action by the Chemical, Life Science, and Associated Scientific Community

10.4.3.1 Building a Culture of Responsibility

Concerned civil society actors—particularly those in the independent chemical and life science communities—should continue fostering a 'culture of responsibility' in science through the endorsement, promulgation, and application of codes of conduct, pledges, and conventions regulating dual-use research—notably the *Hague Ethical Guidelines* for chemists and the *Tianjin Biosecurity Guidelines* for life and associated scientists. The previously under-examined risks of the misuse of toxin and bioregulator

[54] Tucker, J. The body's own bioweapons, *Bulletin of Atomic Scientists*, Volume 64, number 1, March/April 2008, pp. 16–22 & 56–57.

[55] Tucker, J. (2008) op. cit.

research should be given adequate attention. Similarly, attention should focus upon initiatives explicitly combatting the misapplication of toxin and bioregulator research by State weapons programmes. Complementary activities include promoting the non-participation in and "whistleblowing" on toxin and bioregulator weapons programmes; and education and awareness-raising amongst scientific communities, State officials and the general public of the dangers of such development and use. Coordination of all such activities by chemists and life scientists will be vital to their success, firstly to avoid any "mixed messaging" in this area where the BTWC and CWC overlap, and secondly to ensure the most effective use of limited financial, temporal, and personnel resources. The OPCW's Advisory Board on Education and Outreach may prove a useful forum for such coordination.

10.4.3.2 Developing Guidance on Security Implications of Toxin and Bioregulator Research

Attempts to develop appropriate guidance for those conducting dual-use research in the life and associated sciences have been underway for almost two decades but have almost exclusively focused on genetic engineering of pathogens, despite much wider issues being flagged up by the US Academy of Sciences Lemon-Relman report in 2006.[56] This leaves scientists working in other relevant, fast evolving, fields of research—such as the study of toxins, bioregulators and associated physiological systems—in difficulties judging just how much dual-use concern there might be about their work and what they should do to help minimise the risks of its malign application. National and international scientific associations should establish mechanisms to explore these issues, incorporating involvement and active engagement between, security experts and researchers from the relevant scientific disciplines, to inform both communities and collectively develop appropriate guidance for all those engaged in undertaking, funding, publishing, and regulating dual-use toxin and bioregulator research.

10.4.3.3 Monitor and Respond to Science and Technology Developments of Concern

Independent chemical and life scientists and professional organisations should engage in technology monitoring, identifying current activities of concern, specifically highlighting existing research and development of

[56] National Research Council (2006) op. cit.

toxin and bioregulator weapons and associated means of delivery conducted by State entities or other actors. Independent scientists should also undertake technology horizon-scanning to identify and predict likely research trajectories in relevant scientific disciplines and related technologies, highlighting potential application for weapons development programmes. Informed by such monitoring and horizon-scanning, chemical and life science bodies—notably IUPAC and the Inter-Academy Partnership—should constructively engage with the OPCW, BTWC ISU, and individual BTWC and CWC States Parties to raise specific activities of concern; highlight existing limitations in the Conventions and attendant control regimes; and promote possible science-informed policy responses.

Correction to: Toxin and Bioregulator Weapons

Correction to:

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9

This book was inadvertently published without updating the following corrections:

Chapter 3
Page 53: shift reference "Gao, S. et al. (2021)" from last line to fifth line after "…venom from the scorpion Mesobuthus martensii."

Chapter 4
Page 71: delete sentence "The chapter will examine indications…CNS-acting chemicals."

The updated original versions of the chapters can be found at
https://doi.org/10.1007/978-3-031-10164-9_3
https://doi.org/10.1007/978-3-031-10164-9_4
https://doi.org/10.1007/978-3-031-10164-9_8
https://doi.org/10.1007/978-3-031-10164-9_9

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9_11

Page 78:
Line 6 - replace “aerosolized” with “aerosolization”
Line 10 - replace “aerosolized” with “weaponization”
Last line - after “including” add “with regard to”

Chapter 8
Page 166: First line - delete “give space”

Chapter 9 Page 199, Fig 9.1:
2nd column: change “Industrial Chemicals“ to “Industrial and Pharmaceutical Chemicals”
3rd column: insert “PAVA” after “CR”
5th column: change “Biological Weapons” to “Bioregulator Weapons”
6th column: change “Modified toxin weapons” to “Modified and chimeric toxins”
7th column: change “New chimeric toxin and biological agent weapons” to “New chimeric biological agents”
8th column: replace “Anthrax” with “Bacteria, Viruses, Fungi, Rickettsiae”

Appendix: Formal Responses from China, Iran, Russia, Syria, and the US to Information Requests from the University of Bradford Concerning Toxin and Bioregulator Research of Potential Dual-Use Concern

Formal Response from the Permanent Mission of the People's Republic of China to the OPCW

29 October 2021

Dear Dr Crowley,

This is Qian Wang writing from the Permanent Mission of China to the OPCW. Thank you for your letter and for reaching out to us. Thank you for your interests in the implementation of the two important disarmament legal instruments, the Chemical Weapons Convention (CWC) and the Biological and Toxin Weapons Convention (BTWC). We welcome the contributions made by civil society in promoting the realization of the purpose and objective of the above-mentioned Conventions. I would like to take this opportunity to share with you some of our positions and facts regarding China's implementation of the CWC.

Firstly, China has faithfully fulfilled its obligations under the CWC and honored its commitments. China has submitted its various categories of initial and annual declarations to the OPCW in a timely and comprehensive manner pursuant to the provisions of the CWC. All the activities for protective purposes carried out by China are consistent with the provisions of the CWC and are subject to verification and supervision of the OPCW.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9

Regarding the States Parties' obligation under Paragraph 4 of Article X, China has submitted information on its national programme for protection against chemical weapons since 2012. You can find more detailed information in the Report by the Director-General of the OPCW on the Status of the Implementation of Article X of the CWC (EC-98/DG.3, dated 30 June 2021).

The Chinese Government promulgated successively and put into effect the Regulations of the People's Republic of China on the Administration of Controlled Chemicals (1995), the List of Controlled Chemicals by Category (1996), the Rules of Implementation for the Regulations of the People's Republic of China on Controlled Chemicals (1997), and the List of Items Newly Included in Category Three of Controlled Chemicals (1998). These documents have provided a legal framework for the implementation of the CWC and established comprehensive regime of effective administration of the production, trading, use, stockpiling, import and export of scheduled chemicals. In order to prevent and prosecute acts that use substances like toxic chemicals to carry out terrorist activities, the Standing Committee of the National People's Congress of China passed, in December 2001, Amendment No.3 to the Criminal Law of the People's Republic of China, which explicitly criminalizes acts that illegally manufacture, transport, stockpile, or use toxic/poisonous substances to endanger public safety, and has specified corresponding penalties.

China has all along advocated responsible scientific research, and has promulgated a series of domestic laws and regulations to regulate research activities. Those include but not limit to the Law of the People's Republic of China on Progress of Science and Technology (2007), the Biosecurity Law of the People's Republic of China (2020), the Interim Provisions on Addressing Irregularities in Scientific and Technological Activities (2020, unofficial translation) and etc. Chinese scientists have also constructively participated in the drafting of the Hague Ethical Guidelines and the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists, with a view to promoting responsible conduct in science research and to guarding against the misuse of science and technology.

Secondly, with regard to the research on bioregulator and toxin in the case study. As I am not familiar with the scientific research mentioned in your report, I seek your understanding for not commenting on that. However, I'd like to draw your kind attention to the Report of the Scientific Advisory Board on Developments in Science and Technology for the Fourth Special Session of the Conference of the States Parties to

Review the Operation of the CWC(RC-4/DG.1,dated 30 April 2018), in which the paragraph 110 and 111 under Annex 1 mention the following, "A range of detection and identification methods for toxins have been developed by expert laboratories. …Some of these issues are to be addressed by the European programme for the establishment of validated procedures for the detection and identification of biological toxins (EuroBioTox), which involves 23 European laboratories and began in June 2017. … The SAB commends the OPCW for initiating biotoxin analysis exercises. The objectives of these exercises are to improve capabilities for analysis; work toward recommended methods; establish a framework, including reporting, identification, and evaluation criteria for future PTs; assess the advantages and disadvantages of different analytical methods; and develop acceptable criteria for the identification of biological toxins, where biological functionality may need to be characterised." We could tell from the above paragraphs that the detection and identification research on toxins has been carried out by many States Parties and the SAB welcomed the efforts of the Technical Secretariat of OPCW to conduct biotoxin exercises in which two Chinese laboratories have also participated.

Regarding the risk of misuse of bioregulators, I also would like to quote the SAB report (RC-4/DG.1), in which the paragraph 119 under Annex 1 writes "As concluded by the TWG on convergence, the SAB views that the potential of peptides for development as incapacitating agents may have been overstated by some commentators. Peptides could be produced using metabolic engineering and synthetic biology but the pharmaceutical industry currently regards chemical synthesis, using specialised equipment, as the most cost-effective method for producing small peptides. The threat of possible misuse of this technology with regard to the Convention is currently considered low."

Thirdly, as for the Compliance Report issued by the US State Department, I'd like to highlight the following points. In recent years, the US has been making up the so-called annual report on Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments, making wanton comments on other countries' arms control and non-proliferation policies while exalting its own "exemplary" behavior. It is nothing but a threadbare ploy it uses to deflect international attention and malign other countries. The allegation against China is groundless. China has always been firmly opposed to this. I hope Bradford University is a responsible and objective research

institution. I trust you and your team will conduct research based on credible materials, not quoting the reports that deliberately smear other States Parties for political purposes.

Finally, I would like to take this opportunity to bring your attention to the fact that China is a victim of chemical weapons. The chemical weapons abandoned (ACW) by Japan on the territory of China have been posing a grave threat to the lives and property of the Chinese people and the environment. Besides, the only remaining Possessor State of chemical weapons has yet to complete the destruction of all its chemical weapons stockpiles, which constitutes a real threat to the Convention and the world. It would be highly appreciated if your team could pay attention to it and urge the relevant States Parties to effectively implement their Treaty obligations.

I hope you find the above information helpful.

Best regards,

Qian WANG
First Secretary
Permanent Mission of the People's Republic of China to the OPCW
Willem Lodewijklaan 10
2517 JT, The Hague

Formal Response from the Permanent Mission of China to the UN in Geneva

2 November 2021

Dear Dr. Crowley,

Hope this email finds you safe and well.

Thank you for your emails and interest in China's policy on biological and chemical issues. In order to facilitate your research in good faith, our mission would like to share below information and observations, which in no way represents or implies endorsement of the report.

China has all along implemented its obligations under the BWC (The Biological Weapons Convention) in a comprehensive and earnest manner. In accordance with the decision adopted by the Second Review Conference of BWC, since 1988, China has submitted its confidence-building measures in a timely manner. (See the BWC factsheet of Chinese Foreign Ministry)

China takes active actions to regulate the risk of biotechnology research and development, and advocates for responsible biological research. In their recent joint statement on strengthening the BWC, the foreign

ministers of China and Russian Federation "stress(ed) that the rapid development of science and technology in BWC-related areas call for greater attention of the BWC States Parties. There is a need to raise awareness of the risks associated with dual-use research and, simultaneously, promote the full use of the latest advances in biotechnology for peaceful purposes."

The **Biosecurity Law** of China, issued in 2020 and entered into force on 15 April 2021, contains a chapter specifically dedicated to "biotechnology research, development, and application", which clearly demonstrated China's legislative endeavor on this matter.

Based on the joint initiative by China and Pakistan under the BWC framework, Tianjin University and Johns Hopkins Center for Health Security, together with scientists from 21 countries and in close liaison with the Chinese Ministry of Foreign Affairs and the US Department of State, developed **the Tianjin Biosecurity Guidelines for Codes of Conduct for Scientists**, which was subsequently adopted by the InterAcademy Partnership (IAP). **The Tianjin Guidelines** gained overwhelming support in the most recent Meetings of Experts of the BWC.

The facts provided above only reflect a small fraction of China's political, legislative and practical efforts in related areas. We regret to see that the draft text of the case study ignores China's dedicated efforts in implementing and strengthening the BWC, and makes reference to some partial or biased reports that were prepared with the intention to smear China by certain parties. A comprehensive and thorough approach of research in this field is highly encouraged.

We hope these could contribute to your research.

With best regards,

Disarmament Team, Permanent Mission of China to Geneva

Formal Response from the Permanent Mission of the Islamic Republic of Iran to the United Nations Office and Other International Organizations in Geneva

3 June 2022

Dear Professor Dando,

This is to inform you that this Mission did not receive the email from you on 12 May 2022 and indeed the first email was received on 25 May 2022.

It should be emphasized that the content of your article is not substantiated. Having comments on the several allegations raised in your article requires more time.

Generally speaking, Iran as a victim of the WMD that was used by Iraq in the 1980s, with the accomplice of the U.S. and some European countries, believes that the only guarantee against the use or threat of use of WMD is their total elimination.

Confirmation upon receipt of the email would be highly appreciated.

Best Regards

Permanent Mission of the Islamic Republic of Iran to the United Nations Office and other International Organizations in Geneva
Chemin du Petit-Saconnex
28, 1209 Geneva
Tel. +41 22 332 21 00
Fax. +41 22 733 02 03

Formal Response from the Russian Delegation to the UN Conference on Disarmament

20 October 2021

Dear Sir,

Thank you for your letter of October 7, 2021.

The activities of the Russian Federation in medical and biological sphere are exclusively peaceful and fully comply with the Biological and Toxin Weapons Convention (BWC). This is annually confirmed by the information provided within the BWC confidence building measures.

The Russian Federation is consistently advocating the strengthening of the BWC including by adopting a legally binding protocol thereto on the effective verification mechanism which would enable to confirm States-Parties' compliance with their obligations under the BWC. Pending the 9th BWC Review Conference it would be much required to consolidate efforts by States Parties and international academia in this regard.

Apart from that we would like to note that chemicals affecting the central nervous system (CNS-chemicals) are not covered by the CWC. Our position on this issue is laid out in detail in national documents EC-93/NAT.6 and EC-96/NAT.6 published on the CWC website. The consultations among the CWC States Parties in OPCW since 2008 on the CNS-chemicals and its elaboration by OPCW Scientific Advisory Board (which

is far from completion) have shown that this topic requires comprehensive research and examination rather than imposing by certain countries of their own interpretation of the Convention.

Best regards,

Russian Delegation to the Conference on Disarmament

Formal Response from the Permanent Mission of Syria to the OPCW

29 May 2022

Dear Mr. Crowley,

We hope that this e-mail finds you well,

With reference to the below attached e-mail, kindly find the response of the Permanent Mission of the Syrian Arab Republic to your inquiry:

- The Syrian Arab Republic has fulfilled all of its obligations due to its accession to the CWC.
- The Syrian Arab Republic has effectively and fully destroyed its entire chemical weapons stockpile in coordination with the Technical Secretariat of the OPCW, and in accordance with the Chemical Weapons Convention (CWC), and has done so in record time that is unprecedented by any other member state, despite the very challenging and difficult circumstances which Syria has undergone.
- All of the detailed information relating to the Ricin production programme has been fully shared with the Technical Secretariat of the OPCW, and in accordance with the CWC, through declaring the mentioned programme and its strategy, as well as fully disclosing the Ricin production amounts and dates, as well as the dates of their destruction.

Best Regards,

Permanent Mission of Syria to the OPCW

President Kennedylaan 19, 2517JK

The Hague, The Netherlands

Tel: 070-7621040

Formal Response from the Executive Director, US Department of State Bureau of Arms Control, Verification and Compliance, US National Authority for the Chemical Weapons Convention, NACS #202 \058

9 November 2021

Dear Dr. Crowley,

Thank you for your recent letters to Ambassadors Manso and Wood and the opportunity to review and comment on your upcoming publication on the study into bioregulators and toxin weapons.

As noted in previous correspondence, the United States is not developing, producing, stockpiling, or using pharmaceutical-based agents. Accordingly, the United States maintains that this issue is of significant concern. The United States was pleased by the recent adoption of the CNS-acting chemicals decision at the March Executive Council session and expects a similar positive outcome from the November Conference of the States Parties.

Regarding your question related to specific U.S. research, I would refer you to the U.S. Department of Defense and other relevant entities. Additionally, U.S. annual Compliance Report to the Congress, along with Condition 10(C) Report, both underscore current U.S. concerns related to other counties' weaponization of bioregulators and toxin issues under the BWC and CWC and the CNS-acting chemicals issue under the CWC.

Yours Sincerely

Laura. J. Gross

Executive Director

United States Department of State Bureau of Arms Control, Verification and Compliance U.S. National Authority for the Chemical Weapons Convention,

Washington, D.C. 20520

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[1] Note: Page numbers followed by 'n' refer to notes.

M. Crowley, M. R. Dando, *Toxin and Bioregulator Weapons*, Global Issues, https://doi.org/10.1007/978-3-031-10164-9