Threat of non-traditional agents: a new frontier in chemical weapons concerns?

Adrián Repilado-Álvarez [1,2], J A Guerra Guirao [2], I Cuadrado Berrocal [2], M T Llorente Ballesteros [3]

[1]Toxicology Institute of the Defence (ITOXDEF), Madrid, Spain
[2]Department of Pharmacology, Pharmacognosy and Botany, Complutense University of Madrid Faculty of Pharmacy, Madrid, Spain
[3]General Pharmacy Subinspectorate, General Health Inspectorate, Ministry of Defence, Madrid, Spain

Correspondence to
Adrián Repilado-Álvarez; adrirepi@ucm.es

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ABSTRACT

The development and use of chemical and toxin-based weapons have evolved significantly over time, from early historical applications to modern incidents involving highly potent agents. Despite the establishment of international treaties such as the Chemical Weapons Convention (CWC) and the Biological and Toxin Weapons Convention (BTWC), emerging threats posed by non-traditional agents, particularly central nervous system (CNS)-acting chemicals and biotoxins, present ongoing challenges. These substances, while not individually scheduled, fall within the broader definitions of toxic chemicals and are prohibited if used for purposes inconsistent with the conventions.

CNS-acting chemicals, including pharmaceutical-based agents such as fentanyl analogues and alpha-2 adrenergic agonists, raise concerns due to their incapacitating or lethal effects, potential misuse in law enforcement contexts and increasing availability via illicit markets. Biotoxins such as ricin and saxitoxin, although naturally derived, have military relevance and are subject to regulation under both the CWC and BTWC.

This analysis synthesises key developments that have shaped the current threat landscape and explores the challenges these agents pose for both verification mechanisms and military medical preparedness. It highlights gaps in toxidrome identification, limitations in available countermeasures and the need for improved diagnostic capabilities, all of which are critical for mitigating the risks associated with exposure to non-traditional agents.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Toxic chemicals are banned as weapons under international law.
⇒ All declared traditional chemical weapons have been destroyed.
⇒ Concerns remain about non-traditional agents like CNS-acting chemicals and biotoxins.

WHAT THIS ANALYSIS ADDS

⇒ This analysis provides a concise overview of non-traditional agents.
⇒ It highlights their risks, including verification gaps and clinical challenges.
⇒ It also suggests how substance misuse cases may offer valuable insights into toxidromes and possible medical countermeasures.

HOW THIS ANALYSIS MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ This analysis supports strengthening verification systems, especially analytical capacity for non-traditional agents.
⇒ It calls for reassessing their risks and promoting research on countermeasures.

INTRODUCTION

Throughout history, toxic substances have been employed in various forms of conflict, ranging from traditional warfare to more recent acts of terrorism. The origins of chemical weapons can be traced back to early human practices in hunting, fishing and pest control, where poisoned arrows and noxious smoke were commonly used.[1] Over time, these methods were adapted and integrated into military strategies in ancient warfare.

During World War I, the scarcity of conventional munitions, combined with advancements in the chemical industry, further accelerated the development and use of toxic agents.

Despite broad international condemnation, the advancement of chemical weapons did not cease. The Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and their Destruction (Chemical Weapons Convention, the Convention, CWC) officially came into force on 29 April 1997, with the Organisation for the Prohibition of Chemical Weapons (OPCW) tasked with overseeing its implementation.

Toxic chemicals are categorised into three schedules based on their potential risk to the objectives of the Convention, which in turn determines the verification measures required for their control. Despite the enforcement of the CWC, chemical attacks have still occurred in recent decades, such as the use of sarin in Syria in 2013, and the 2018 Salisbury poisonings where the nerve agent Novichok was employed.[2 3]

Recently, the last chemical weapon from the stockpiles declared by all States Parties to the CWC was destroyed on 7 July 2023.[4] However, the threat of the use of chemical weapons remains. Among the most significant current risks is the potential use of so-called non-traditional chemical agents, such as central nervous system (CNS)-acting chemicals and biotoxins.[5] These types of agents, although not included in the schedules, are considered toxic chemicals, as they are capable of causing death, temporary incapacitation or permanent harm, and therefore pose a risk of potential misuse as weapons.

This analysis, based on a literature review and documents from the OPCW, focuses on the emerging challenges posed by CNS-acting chemicals and

biotoxins and their implications for military medical preparedness and the verification mechanisms.

DISCUSSION

Definitions

The CWC employs the term 'toxic chemical' to denote '*any chemical which, through its chemical action on life processes, can cause death, temporary incapacitation or permanent harm to humans or animals*'. The term 'chemical weapon', on the other hand, refers to toxic chemicals and their precursors, and to munitions, devices and equipment specifically designed to weaponise or to be used directly in connection with toxic chemicals.

The CWC excludes from the definition of a chemical weapon those purposes not prohibited under the Convention, provided that the types and quantities of chemicals used are consistent with such purposes. One such purpose is law enforcement, including domestic riot control purposes. 'Riot Control Agents' (RCAs) are defined as '*any chemical not listed in a Schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure*'. According to the Convention, RCAs are prohibited as a method of warfare and if the types or quantities employed are inconsistent with their intended purpose, they would no longer be exempt from the definition of a chemical weapon.[6]

However, some experts argue that further clarification is needed regarding the interpretation of 'law enforcement purposes', particularly in determining which types and quantities of chemicals can be considered consistent with such use.[7 8]

CNS-acting chemicals

In recent years, the Scientific Advisory Board (SAB) of the OPCW has raised concern over a group of compounds acting on the CNS.[9] This group includes a variety of substances such as anaesthetics, sedatives, analgesics and other agents originally developed for medical purposes, collectively referred to as pharmaceutical-based agents. Many of these substances may also be classified as dual-use agents, given their legitimate therapeutic applications alongside their potential misuse as chemical weapons.

Some of these compounds may exhibit lethality comparable to that of traditional nerve agents, such as S-[2-(diisopropylamino) ethyl] methylphosphonothiolate (VX). Notable examples include alpha-2 adrenergic agonists such as clonidine and medetomidine, inhalational anaesthetics like isoflurane and sevoflurane, and potent opioid analgesics such as carfentanil.

The potential application of CNS-acting chemicals as chemical agents, often misleadingly referred to as 'non-lethal', has attracted attention in several countries due to their incapacitating effects. In certain cases, research involving these incapacitating chemical agents (ICAs) has been conducted under the justification of defensive or scientific purposes.[10]

The North Atlantic Treaty Organization doctrine identifies ICAs, encompassing both mental and physical types, as one of the principal categories of chemical effects associated with traditional chemical agents, a classification under which RCAs may also be included. However, among the substances with incapacitating effects, only 3-quinuclidinyl benzilate is currently listed in the schedules of the CWC. In contrast, other chemicals with similar effects, such as CNS-acting compounds, are not individually scheduled. Nevertheless, these substances, considered toxic chemicals under the CWC, would fall under the definition of a chemical weapon if used for purposes other than those not prohibited by the Convention.[11]

The classification of ICAs as RCAs for law enforcement purposes would be inconsistent with the definition provided by the Convention, as the effects of these agents depend on multiple factors, particularly dosage, exposure conditions and individual susceptibility. Individual susceptibility depends on factors such as age, weight, sex, pre-existing medical conditions and drug interactions, while exposure is determined by agent concentration and duration. This reflects the toxicological principle famously articulated by Paracelsus: '*sola dosis facit venenum*'—it is only the dose that makes the poison.

In the case of CNS-acting agents, it is not possible to guarantee that the '*disabling physical effects*' would '*disappear within a short time following termination of exposure*'. A notable example highlighting this concern is the use of carfentanil and remifentanil by the Russian security forces during the Dubrovka theatre hostage crisis in Moscow in 2002, which resulted in the death of at least 123 hostages, reportedly due to overdose resulting from exposure to the incapacitating agents.[12]

Since 2003, the SAB of the OPCW has highlighted risks posed by CNS-acting chemicals, emphasising their narrow safety margin and the emergence of new delivery methods that hinder dose control.[13 14]

On 1 December 2021, the decision to prohibit the aerosolised use of CNS-acting chemicals for law enforcement purposes was adopted by the OPCW Conference of States Parties.[15] However, not all Member States have agreed with this decision.[16]

In this context, during the 2024 sessions of the Executive Council of the OPCW, discussions took place regarding the alleged development of research programmes involving pharmacological agents, specifically medetomidine, for potential use as weapons.[17]

In addition to the lack of consensus among States Parties regarding the interpretation and application of existing regulations on the use of CNS-acting chemicals for law enforcement purposes, there is growing concern over their increasing misuse as substances of abuse (ie, fentanyl analogues and medetomidine).[18 19] This trend suggests that access to these compounds via illicit markets is not uncommon, which could, in turn, facilitate their acquisition by non-state actors, including terrorist groups.

Clinical management of intoxications involving these substances in the context of abuse can provide valuable insights into risk assessment, toxidrome characterisation and evaluation of therapeutic alternatives. For instance, key lessons derived from such cases include: naloxone doses required to reverse carfentanil intoxication may be higher than those used for other fentanyl analogues[20]; its effectiveness against alpha-2 adrenergic agonists remains uncertain[21]; and alternative antidotes such as the alpha-2 adrenoceptor antagonist atipamezole, though not approved for human use, may offer potential therapeutic value.[22] Together, these clinical nuances highlight the need to better understand toxicological profiles and guide the development of appropriate medical countermeasures for CNS-acting chemicals.

Given the sequence of developments outlined above, important questions arise: are the current verification mechanisms under the CWC sufficiently prepared to detect, regulate and prevent the weaponisation of non-traditional chemical agents?

Equally important is the question of whether Member States possess adequate treatment protocols, toxidrome identification guidelines and access to effective antidotes to manage the medical consequences of exposure to these non-traditional agents. This should be complemented by a forward-looking consideration of the adequacy of existing personal protective

equipment and decontamination procedures in the face of the distinct and evolving threats posed by such agents.

These questions point to the need for continued dialogue among States Parties and greater transparency in research involving CNS-acting agents to ensure that the Convention remains effective when considering evolving scientific and technological realities.

Biotoxins

Biological toxins are poisonous substances produced by animals, plants or microbes. Broadly, they can be classified into two main categories based on their mechanism of action: neurotoxic and cytotoxic. These effects have historically attracted interest in their potential military applications, as lethal agents and as the so-called non-lethal weapons, including incapacitating agents and RCAs.[23]

However, the use of these compounds as weapons is prohibited under both the CWC and the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (Biological and Toxin Weapons Convention or BTWC). This treaty entered into force on 26 March 1975. With respect to toxins, States Parties have agreed never, under any circumstances, to develop, produce, stockpile or otherwise acquire or retain '*…toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes*', as well as any weapons, equipment or means of delivery designed to use such substances for hostile purpose or in armed conflicts.[24]

Among the main concerns raised over the past decade regarding potential limitations of this treaty are the lack of a clear distinction between peaceful and hostile purposes, the absence of an effective compliance verification mechanism and the need to address advances in biotechnology.[25–27]

There have been documented cases in the past involving the use of ricin, and it is well known that, during the 1970s, research programmes were conducted on marine toxins such as saxitoxin.[28] This has led to the inclusion of ricin and saxitoxin in the schedule I of the CWC.

At the international level, alongside the OPCW, the United Nations Secretary-General's Mechanism for the Investigation of Alleged Use of Chemical, Biological or Toxin Weapons (UNSGM) also holds a mandate related to biotoxins. In 2021, the OPCW and UNSGM supported the creation of a Temporary Working Group (TWG) on Biotoxin Analysis, which concluded that the ability to detect, identify and characterise such non-traditional agents in samples during OPCW-led investigations is essential. To strengthen this capacity, the TWG recommended developing proficiency testing for biotoxins, modelled on those established for traditional chemical agents in environmental and biomedical samples.[29]

Beyond verification, these analytical capabilities are also clinically valuable, supporting diagnosis and treatment after biotoxin exposure.

However, given the wide diversity of molecules that may pose a risk of being used as weapons, both traditional and non-traditional agents (including CNS-acting chemicals and biotoxins), it remains a significant challenge for any single laboratory to possess the necessary expertise and analytical capabilities to detect and analyse all of them.

This limitation underscores the need for international cooperation and specialised laboratory networks to strengthen verification mechanisms. Integrating biotoxin capabilities into BTWC and OPCW frameworks is essential for preparedness, attribution and response to alleged toxin weapon use.

CONCLUSIONS

The emergence of non-traditional agents such as CNS-acting chemicals and biotoxins challenges verification mechanisms under the CWC and BTWC. Despite falling within the scope of these conventions, gaps remain in the terminology employed in the treaties, detection capabilities and compliance verification. In addition, these agents also pose clinical concerns. Accurate diagnosis, toxidrome characterisation and effective countermeasures are crucial for mitigating health impacts. Strengthening international cooperation, expanding laboratory networks and updating technical guidelines are essential to address these limitations. Recent initiatives, such as the TWG on Biotoxin Analysis, demonstrate progress, but further efforts are needed to ensure preparedness in the face of evolving scientific and technological threats.

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ORCID iDs
Adrián Repilado-Álvarez http://orcid.org/0000-0002-2107-9999
J A Guerra Guirao http://orcid.org/0000-0002-0497-1061
I Cuadrado Berrocal http://orcid.org/0000-0003-0727-9633
M T Llorente Ballesteros http://orcid.org/0000-0003-2600-8046

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