

## REVIEW

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# 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†

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Compounds that cause powerful sensory irritation to humans were reviewed by the Scientific Advisory Board (SAB) of the Organisation for the Prohibition of Chemical Weapons (OPCW) in response to requests in 2014 and 2017 by the OPCW Director-General to advise which riot control agents (RCAs) might be subject to declaration under the Chemical Weapons Convention (the "Convention"). The

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chemical and toxicological properties of 60 chemicals identified from a survey by the OPCW of RCAs that had been researched or were available for purchase, and additional chemicals recognised by the SAB as having potential RCA applications, were considered. Only 17 of the 60 chemicals met the definition of a RCA under the Convention. These findings were provided to the States Parties of the Convention to inform the implementation of obligations pertaining to RCAs under this international chemical disarmament and non-proliferation treaty.

## 1. Introduction

The Chemical Weapons Convention (hereinafter, the 'Convention')<sup>1</sup> is an international disarmament and non-proliferation treaty banning chemical weapons.<sup>2</sup> It entered into force in 1997 and today has 193 States Parties (nations party to the treaty). This leaves only 4 States currently outside its obligations: the Democratic People's Republic of Korea, Egypt, Israel, and South Sudan.

The Organisation for the Prohibition of Chemical Weapons (OPCW),<sup>3,4</sup> an international organisation based in The Hague, in The Netherlands, is the implementing body of the Convention. In 2013, the OPCW was awarded the Nobel Peace Prize (Fig. 1) for its extensive efforts to eliminate chemical weapons.<sup>5</sup> The main objective of the OPCW is to realise a world free of such weapons.

Each State Party to the Convention undertakes never under any circumstances to (a) develop, produce, otherwise acquire, stockpile or retain chemical weapons, or transfer, directly or indirectly, chemical weapons to anyone; (b) use chemical weapons; (c) engage in any military preparations to use chemical weapons; or (d) assist, encourage or induce, in any way, anyone to engage in any activity prohibited to a State Party under the Convention.<sup>1</sup> The States Parties are also obligated to declare and destroy any chemical weapons and related production facilities they may possess.

Additionally, States Parties are prohibited from using riot control agents, for example "tear gases", as a method of warfare. Law enforcement, including domestic riot control, is not subject to this prohibition under the Convention, as RCA use is governed under the national laws of the State Parties. States Parties are however, obligated to declare any chemicals they hold for riot control purposes, specifying the chemical name,

structural formula, and Chemical Abstracts Service (CAS) registry number, if assigned. Sensory irritants were suggested as weapons during the American Civil War of 1861–1865,<sup>6</sup> and were the first chemicals to be deployed in the First World War of 1914–1918 (starting with ethyl bromoacetate).<sup>7,8</sup> Since then, there has been a rich history of their research and development as RCAs for law enforcement.<sup>9–14</sup>

The Convention defines "chemical weapons" in its Article II(1). They comprise, together or separately: (a) toxic chemicals and their precursors, except where intended for purposes not prohibited by the Convention, as long as the types and quantities are consistent with such purposes; (b) munitions and devices, specifically designed to cause death or other harm through the toxic properties of those toxic chemicals specified in (a) above, which would be released as a result of the employment of such munitions and devices; and (c) any equipment specifically designed for use directly in connection with the employment of munitions and devices specified in (b) above.<sup>1</sup>

Articles II(2) and II(3) of the Convention define respectively a "toxic chemical" and a "precursor" as follows:

- Toxic chemical. 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.<sup>1</sup>

- Precursor. Any chemical reactant which takes part at any stage in the production by whatever method of a toxic chemical. This includes any key component of a binary or multicomponent chemical system.<sup>1</sup>

The Convention prohibits the use of all toxic chemicals as a means of warfare (such chemicals being defined by their action on life processes in humans and animals, *vide infra*). For implementing the Convention, toxic chemicals and precursors, which have been identified as being particularly relevant for the application of verification measures, are listed in three Schedules in the Convention's Annex on Chemicals,<sup>1</sup> as described elsewhere.<sup>2,15,16</sup>

With regard to RCAs, the Convention does not refer to any specific chemicals. It only defines an RCA, in its Article II(7), 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.'<sup>1</sup>

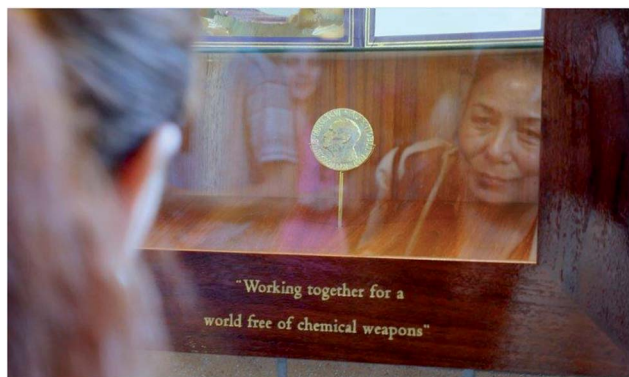


Fig. 1 The Nobel Peace Prize awarded to the OPCW in 2013.



## 2. The OPCW Director-General's request

The definition of an RCA in the Convention leaves room for interpretation as to which chemicals would meet the requirements. To provide a point of reference to support declarations from States Parties, the OPCW Director-General requested advice from the OPCW Scientific Advisory Board (SAB)<sup>17–23</sup> (Fig. S1†), at its Twentieth Session in June 2013,<sup>24</sup> on which RCAs would be subject to declaration under the Convention.

As States Parties are required to declare RCAs, the Director-General wished to assemble an indicative list of substances that, from a technical viewpoint, would be consistent with the Convention's definition of an RCA. This list, which would not be exhaustive, would be made available to States Parties to provide guidance on the issue. An initial list had been developed by the OPCW, taking into account (a) all RCAs that had been declared since entry into force of the Convention‡; (b) previous considerations from the SAB§; and (c) an initial survey¶ conducted by the OPCW in 2013 of RCAs that had been researched or were available for purchase. The SAB was asked to consider this initial list and provide technical advice on:

- (a) Whether the list reflected the then current RCAs that could be considered as declarable in accordance with Article III(1)(e); and, in particular;
- (b) The soundness of the criteria used by the OPCW in drawing up the initial list;
- (c) Which other considerations or criteria, if any, should be used in developing the list;
- (d) Which chemicals, if any, should be deleted from the list; and
- (e) Which chemicals, if any, should be added to the list?

This paper describes the response of the SAB to the Director-General's request,<sup>24</sup> summarising the analysis, results, conclusions, advice given, additional and future considerations, and prospects and recommendations. It follows other advice delivered by the Board<sup>25–30</sup> to the Director-General and States Parties, which is intended to strengthen the norm against the use of

chemical weapons and to prevent any possibility of their re-emergence.

## 3. Analysis

Noting that the requested advice was specific to RCAs and aimed at identifying chemicals that met the specific criteria defined under Article II(7) of the Convention, the SAB considered that the definition of any prospective RCA hinged on whether it caused a rapid and reversible irritation or disabling physical effects that disappeared shortly after exposure. It concluded that a chemical whose effects from acute exposure were potentially irreversible and damaging to life processes, was excluded by Article II(7) from being categorised as an RCA. In assessing the indicative list of RCAs provided by the OPCW, the literature describing the toxicity of each chemical was carefully assessed by the SAB.

Reflecting on the definition of an RCA within the Convention, the SAB noted that the phrase 'can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure' is not defined absolutely and implies a statistical probability of response. Toxicities of chemicals vary in different animal species and by different routes of administration. It is not always possible in the absence of human data to predict accurately from animal data the effects on humans. The Himsworth report<sup>31</sup> into the toxicological aspects of 2-chlorobenzylidenemalononitrile (CS) – probably the most common contemporary "tear gas" – and its use for civil purposes, stated that the effects of any chemical intended for use in internal security operations should be studied in a manner 'more akin to that in which we regard the effects of a new drug'.<sup>31</sup> Unfortunately toxicological studies on many of the chemicals on the initial list of potential RCAs had not been performed to the level of scrutiny a new drug would receive.

In assessing the suitability of each chemical for consistency with the RCA definition within the Convention, previous relevant SAB reports<sup>32–34</sup> and the scientific literature were reviewed. Assessments of the toxicity of RCAs were made based on acute exposure in outdoor scenarios where the chemicals would be present in low dilution in air, in non-enclosed spaces, with the people affected able to escape unimpeded from the irritant cloud. It was assumed that the people irritated by the aerosolised chemicals would be free to evacuate without obstruction immediately from the zone of contamination. It was recognised that very high concentrations of the same chemicals projected into enclosed spaces, and a delayed egress of those exposed, could result in health effects of a greater severity. These effects might, under such circumstances, lead to temporary incapacitation, permanent harm, or even death.<sup>9,13,35</sup> Founded on a scenario involving the dispersal of relatively low concentrations of the chemicals and unrestricted movement after the people would first perceive sensory irritation, a judgement on whether each chemical met the criteria of an RCA, as defined by Article II(7), was made. The reason for the scenario considered is due to reports that under different conditions the use of

† Up to this time, in June 2013, fourteen chemicals had been declared as RCAs by States Parties since the Convention had entered into force in 1997. The SAB was informed by the OPCW of the identity of these chemicals but not which State Parties had declared them, in line with OPCW confidentiality rules.

§ In 2001 the SAB's Temporary Working Group on Analytical Procedures had drawn up a list of RCAs and old/abandoned chemical warfare agents to be considered for inclusion in the OPCW Central Analytical Database (OCAD). For the purposes of implementing the Convention, old chemical weapons are often considered to be chemical weapons produced between 1925 and 1946 that have deteriorated to the extent that they can no longer be used as chemical weapons.<sup>2</sup> With the OPCW Designated Laboratory network providing an off-site sample analysis capability, the OCAD has served as a database for on-site use, especially for inspections to commercial facilities subject to declaration and inspection as part of the industry verification obligations of States Parties.<sup>25</sup> The OCAD includes analytical data for chemicals relevant to the Convention. The 2018 edition of the database contains mass spectra and retention indices for more than 4400 chemicals, nuclear magnetic resonance spectra for nearly 300 chemicals, and infrared spectra for more than 750 chemicals.

¶ The list is not provided here, but did contain those chemicals assessed by the SAB, which appear in Tables S1 and S2 in the ESI.†



certain types of RCAs has been linked to longer term health effects.<sup>9,13,35</sup>

Overall, the SAB considered 60 chemicals that included: (a) 14 declared as RCAs since entry into force of the Convention; (b) chemicals identified as potential RCAs from a list of “riot control agents and old/abandoned chemical weapons” to be considered for inclusion in the OPCW Chemical Agent Database (OCAD) (this list had been drafted by the SAB's Temporary Working Group on Analytical Procedures in 2001 (ref. 32)); (c) the survey conducted by the OPCW in 2013 of RCAs that had been researched or were available for purchase; and (d) 13 additional chemicals which were recognised by the SAB as having potential for RCA applications.

## 4. Results

After the analysis according to the criteria outlined above, the SAB concluded by consensus that:

(a) The list contained current RCAs that could be considered declarable in accordance with the Convention.

(b) The criteria used by the OPCW to draw up the list were sound.

(c) No chemicals needed to be deleted from the list and those which did not match the definition of an RCA were identified.

(d) The chemicals added to the list were those associated in the scientific literature with riot control, and therein their physiological action compared to RCAs, or those having physiological properties that could favour their research or potential use in this regard.

The SAB found that 17 of the 60 chemicals met the RCA definition as defined by Article II(7). Their chemical and toxicological properties and CAS numbers appear in Table S1.† The literature reviewed (Table S1 in ESI†) revealed that most of these 17 chemicals acted by activating the Transient Receptor Potential Ankyrin 1 (TRPA1)<sup>36–40</sup> or Vanilloid 1 (TRPV1)<sup>41–43</sup> ion channels in the peripheral nervous system (PNS), with CS being an example of a TRPA1 activator,<sup>14,36–40</sup> and capsaicin, the main component of chilli peppers imparting irritancy, being an example of a TRPV1 activator.<sup>42,43</sup> Binding to TRPA1 or TRPV1 is thought to play a role in mediating in humans the ‘sensory irritation or disabling physical effects which disappear within a short time following termination of exposure’.<sup>1</sup> There is a growing body of evidence that activation of TRPA1 and/or TRPV1 ion channels is involved in the perception of irritancy in humans and certain animals.

However, of the seventeen compounds identified by the SAB as conforming to the definition of an RCA, seven remain to be proven to activate TRPA1 or TRPV1 receptors. These are 4-nonanolylmorpholine, 2'- and 3'-chloroacetophenone,  $\alpha$ -chlorobenzylidenemalononitrile, *cis*-4-acetylamino-dicyclohexylmethane, *N,N'*-bis(isopropyl)ethylenediimine, and *N,N'*-bis(*tert*-butyl)ethylenediimine. However, these chemicals are reported to produce in humans an immediate sensory irritation that disappears a short time after exposure, and no evidence was found to suggest that they were capable of causing more permanent harm.

## 5. Conclusions

The SAB concluded that the following 17 chemicals met the criteria of a RCA as defined by Article II(7) of the Convention:<sup>44</sup>

- (a) 2-Chloroacetophenone (CN)
- (b) 2-Chlorobenzylidenemalononitrile (CS)
- (c) Dibenz[*b,f*][1,4]oxazepine (CR)
- (d) Oleoresin capsicum (OC)
- (e) 8-Methyl-*N*-vanillyl-*trans*-6-nonenamide (capsaicin)
- (f) 8-Methyl-*N*-vanillylnonanamide (dihydrocapsaicin)
- (g) *N*-Vanillylnonanamide (pseudocapsaicin, PAVA)
- (h) *N*-Vanillyl-9-methyldec-7-(*E*)-enamide (homocapsaicin)
- (i) *N*-Vanillyl-9-methyldecanamide (homodihydrocapsaicin)
- (j) *N*-Vanillyl-7-methyloctanamide (nordihydrocapsaicin)
- (k) 4-Nonanolylmorpholine (MPA)
- (l) 2'-Chloroacetophenone
- (m) 3'-Chloroacetophenone
- (n)  $\alpha$ -Chlorobenzylidenemalononitrile
- (o) *Cis*-4-acetylamino-dicyclohexylmethane
- (p) *N,N'*-Bis(isopropyl)ethylenediimine
- (q) *N,N'*-Bis(*tert*-butyl)ethylenediimine

The SAB concluded also that these 43 chemicals did not meet the criteria of a RCA as defined by Article II(7) of the Convention:<sup>44</sup>

- (a) Acrolein
- (b) 4'-Chloroacetophenone
- (c) 2-Bromoacetophenone
- (d) 2-Bromoethyl acetate
- (e) Ethyl chloroacetate
- (f) Ethyl bromoacetate
- (g) Ethyl iodoacetate
- (h) Chloroacetone
- (i) Bromoacetone
- (j) Iodoacetone
- (k) 1,1-Dichloroacetone
- (l) 1-Bromo-2-butanone (bromomethyl ethyl ketone)
- (m) Bromobenzyl cyanide (CA)
- (n) Benzyl chloride
- (o) Benzyl bromide
- (p) Benzyl iodide
- (q) 2-Methylbenzyl bromide (*o*-xylyl bromide)
- (r) 3-Methylbenzyl bromide (*m*-xylyl bromide)
- (s) 4-Methylbenzyl bromide (*p*-xylyl bromide)
- (t) 2-Nitrobenzyl chloride
- (u) 1,2-Bis(bromomethyl)benzene (*o*-xylylene dibromide)
- (v) 1-Methoxy-1,3,5-cycloheptatriene (CHT)
- (w) (*Z,E*)-Propanethial S-oxide
- (x) Trichloronitromethane (chloropicrin)
- (y) Tribromonitromethane (bromopicrin)
- (z) 1,1,2,2-Tetrachloro-1,2-dinitroethane
- (aa) Phenylimidocarbonyl chloride
- (bb) Phosgene oxime (CX)
- (cc) Methyl chloroformate
- (dd) Chloromethyl chloroformate
- (ee) Dichloromethyl chloroformate
- (ff) Trichloromethyl chloroformate (diphosgene)



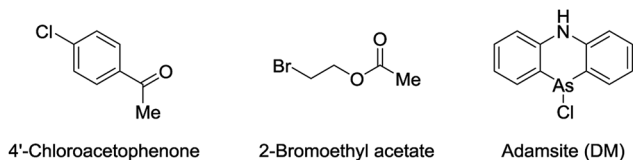


Fig. 2 Chemicals that had seen historic use as RCAs which do not meet the definition of an RCA under Article II(7) of the Convention.

- (gg) Bis(trichloromethyl)carbonate (triphosgene)
- (hh) Methylchloroarsine (MD)
- (ii) Ethylchloroarsine (ED)
- (jj) Phenylchloroarsine (MA)
- (kk) Diphenylchloroarsine (DA)
- (ll) Diphenylcyanoarsine (DC)
- (mm) 10-Chloro-5,10-dihydrophenarsazine (Adamsite, DM)
- (nn) 10-Chloro-5,10-acridarsine (Excelsior)
- (oo) 5(10*H*)Acridarsinecarbonitrile
- (pp) Trialkyl-lead compounds
- (qq) Piperine

Three chemicals that had seen historic use for riot control purposes were found to have harmful properties that placed them on the list of chemicals not meeting the criteria of an RCA. These were 4'-chloroacetophenone, 2-bromoethyl acetate, and 10-chloro-5,10-dihydrophenarsazine (Adamsite, DM). Their structures are given in Fig. 2. The impact of these chemicals on life processes, even in low dilution, was judged by the SAB to be associated with a high probability of causing permanent harm.<sup>44</sup> The conclusion that Adamsite did not meet the criteria of an RCA was consistent with the finding of the SAB in 1999, whereupon it was stated that 'it should no longer be used as an RCA, as it fails to meet today's concerns for safety'.<sup>33,34</sup> Three additional chemicals – *cis*-4-acetylaminodicyclohexylmethane, *N,N'*-bis(isopropyl)ethylenediimine, and *N,N'*-bis(*tert*-butyl)ethylenediimine – were considered in addition to the initial list provided by the OPCW and found by the SAB to conform to the definition of an RCA in the Convention.<sup>44</sup>

The SAB also recognised 43 other chemicals – those on the initial list and 13 additions – that did not align with the definition of an RCA.<sup>44</sup> One of these, trichloronitromethane (CCl<sub>3</sub>NO<sub>2</sub>), features as a toxic chemical on Schedule 3A.04 of the Convention.<sup>1</sup> It is excluded as a RCA, as RCAs are not listed in any of the Schedules.

## 6. Advice

The SAB advised the OPCW Director-General and States Parties in May 2014 that 17 chemicals from the list of 59 it had considered corresponded to a RCA as defined by Article II(7).<sup>45</sup> This list of 17 RCAs was provided to the States Parties as a point of reference in support of their declarations.

Subsequently, the Director-General requested in March 2017 that the SAB re-examine the issue, taking into account all available scientific literature up to March 2017.<sup>46</sup> After the updated review, the list of 17 RCAs remained unchanged, but 43 additional chemicals (the 42 chemical examined previously plus

another: piperine, the major irritant in black pepper), were considered by the SAB at its Twenty-Fifth Session<sup>46</sup> (Fig. S2†) and were provided as a reference list of substances that do not meet the criteria of an RCA (Table S2†) (and should not be declared as such) but may have historically been used, or considered for use, as RCAs.<sup>44</sup> A poster summarising the 17 chemicals found to accord with the definition of an RCA, appears as Fig. S3 (in the ESI),† and is available to download for free from the OPCW public website.<sup>47</sup> In response to the SAB's advice, the OPCW Director-General encouraged States Parties to consider this list of chemicals when they review policies relating to RCAs.<sup>48</sup>

## 7. Additional considerations

RCAs, which produce an immediate and reversible disabling effect on personnel, appear to act primarily on the sensory neurons of the PNS in the eyes, nose, respiratory tract, and skin, and have limited or no direct action on the central nervous system (CNS).<sup>49</sup> However, other types of disabling chemicals, historically termed "incapacitating chemical agents" (ICAs),<sup>50</sup> differ from RCAs as they act primarily on the CNS. ICAs also differ from RCAs in that their effects are not usually confined to sensory irritation of a temporary nature. Compounds exerting a pharmacological effect predominantly on the CNS can induce incapacitation through cognitive impairment and loss of muscle function, and intoxication by them can ultimately result in impaired locomotion, unconsciousness, and possibly death from respiratory arrest (or other CNS damage). Certain groups of individuals are more susceptible to chemicals that act centrally: these include the very young, the aged, and the infirm.

The SAB has, since its Fifteenth Session in April 2010,<sup>51</sup> considered the history of ICAs since the 1950s, including the fact that no chemical has been discovered or developed that satisfies the requirements of being able to produce almost instantaneous incapacitating effects which will last for some hours with no health risks to the exposed individuals.<sup>52,53</sup> The SAB recognises that chemicals that selectively modify CNS functions, such as the opioid fentanyl and its analogues, which are considered to be safe when used under controlled medical conditions, can have very low safety margins when delivered as aerosols, based on factors including uneven dissemination, variability in human response, and a need for rapid onset of action.<sup>54–56</sup> Other examples with a similar profile might include other CNS depressants as well as stimulants. The SAB noted that some fentanyl analogues have lethality comparable to the organophosphorus nerve agent VX.<sup>57–59</sup> In view of these factors the SAB has most recently discussed such compounds as "Central Nervous System-acting chemicals" (or "CNS-acting chemicals") rather than "incapacitants".<sup>49,50</sup>

The use of chemicals for law enforcement has seen discussion that extends beyond chemicals that would qualify as RCAs, specifically with regard to chemicals that can induce incapacitating effects. Such effects that result from an action primarily on the CNS would exclude such chemicals from meeting the definition of an RCA; pertinent examples include fentanyl compounds.<sup>60–63</sup> A lethal dose of carfentanyl, one of the most



potent members of this class, for example, for the average human, is estimated to be only 20 micrograms (20 one-millionths of a gram), an amount barely visible to the naked eye.<sup>64</sup> How to consider such chemicals in the context of the Convention and law enforcement is a topic of policy debate.<sup>49,50</sup> In the interest of moving this debate forward, 39 out of the 193 States Parties jointly published a paper on the aerosolisation of CNS-acting chemicals for law enforcement last year encouraging States Parties 'that have not yet done so to make their positions known, or to express their interest for further discussion, on the use of aerosolised CNS-acting chemicals in law enforcement'.<sup>65</sup>

To aid the policy discourse, the SAB advised that CNS-acting compounds cannot be classed as RCAs, as they do not meet the RCA definition given in Article II(7).<sup>1</sup> An example of the distinction between RCAs and CNS-acting compounds is provided by the RCA materials, CS and dibenzo[*b,f*][1,4]oxazepine (CR), which primarily affect the PNS,<sup>44–47</sup> and two arsenical agents that were used during the First World War to cause sensory irritation and harm to life processes: phenyl-dichloroarsine (MA) and diphenylchloroarsine (DA) (Fig. 3). In contrast to CS and CR, whose irritant effects are short-lived, the latter cause transient irritation, as well as CNS effects, from about 30 min after exposure that can persist for hours and result in permanent physiological damage. The CNS effects can include headache, perspiration, chills, nausea, vomiting, cramps, depression and malaise. MA is also a vesicant (it blisters skin) and produces slow-healing wounds (Table S2†). The SAB discounted these and other arsenical compounds from the initial list from qualifying as RCAs as they can cause systemic poisoning.<sup>14,47</sup>

Note that a CNS-acting chemical, 3-quinuclidinyl benzilate (BZ),<sup>66,67</sup> and its precursors quinuclidin-3-ol (1) and benzoic acid (2) (Fig. 3), are listed in the Convention's Annex on Chemicals under Schedule 2. States Parties possessing these chemicals in certain quantities are required to declare them to the OPCW so that they can be subjected to oversight under the Convention's

verification regime.<sup>1</sup> Small inhaled doses of BZ, an anticholinergic drug once stockpiled as a chemical weapon (whose stockpile has since been destroyed), can cause drowsiness and decreased alertness.<sup>66</sup> Larger doses result in a progressive intoxication: symptoms 1 to 4 h after exposure include ataxia (a loss of control of body movement), blurred vision, confusion, dizziness, dry mouth, sedation, tachycardia (a quickened heart rate), and vomiting, progressing to stupor (a state of near unconsciousness or insensibility). After 4 to 12 h, people affected cannot respond effectively to their environment, or move in a controlled and coordinated way. In 12 to 48 h, increased activity with random unpredictable behaviour is observed, followed by return to normal after 48 to 96 h. The appearance of BZ on the list of chemicals scheduled by the Convention discounts it automatically as an RCA.<sup>44,45</sup>

## 8. Future considerations

Every five years the States Parties convene a Conference to review the operation of the Convention (a 'Review Conference') to which the SAB provides a report on developments in science and technology to assist the States Parties in their deliberations with science advice to better inform decision making. The SAB's report summarises science and technology and scientific advances deemed of relevance to the Convention over the five-year period since the last Review Conference. The report makes recommendations to the OPCW Director-General and States Parties that are intended to further fortify the implementation of the Convention. The next Review Conference, the fourth since entry into force of the treaty, will be held in The Hague in November 2018. The SAB's science and technology report to this conference<sup>54</sup> includes the following recommendations mentioning RCAs and CNS-acting chemicals and advocating inclusion of their analytical information into the OCAD:

- 'Appropriate analytical data for chemicals that may pose a risk to the Convention or that are needed to help differentiate permitted activities from prohibited activities should be added to the OCAD. This could include isotopically-labelled relatives and stereoisomers of scheduled compounds, salts of scheduled chemicals, toxic industrial chemicals, CNS-acting chemicals, riot control chemicals, bioregulators [endogenous chemicals that regulate biological/life processes, such as the neuropeptide substance P], toxins, and unscheduled chemicals that have been identified as posing a risk to the Convention.'<sup>54–56</sup>

- '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 the issue. In view of the increasing availability of such chemicals, the Secretariat [OPCW] 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 (OCAD). This is consistent with previous SAB advice on the subject.'<sup>54–56</sup>

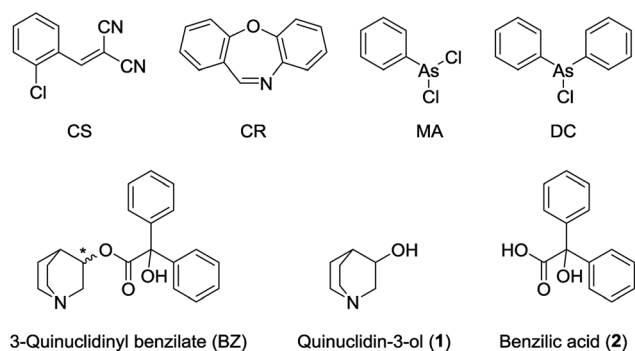


Fig. 3 The RCAs CS and CR are used in law enforcement. The historical arsenicals, MA and DC, were deemed by the SAB not to be RCAs, because of their toxicity to life processes, including to the CNS (top row). The CNS-acting chemical BZ and its precursors 1 and 2 (bottom row). BZ has a stereogenic carbon atom (asterisk). It has been weaponised historically as the racemate, but can exist as two enantiomers, which have different biological potencies.<sup>26</sup>



The SAB Chairperson presented the compiled outcomes of the Board's deliberations since entry into force of the treaty on RCAs and CNS-acting chemicals to States Parties during the Twenty-Second Session of the Conference of States Parties, in November 2017.<sup>52,53</sup> In reply to the SAB's report on developments in science and technology to the Fourth Review Conference,<sup>54</sup> including the two aforementioned recommendations, the OPCW Director-General expressed support to all the SAB's recommendations (of which there are many) and pointed out their value to the States Parties of the Convention.<sup>68</sup>

The advice on RCAs and CNS-acting chemicals,<sup>44,45</sup> the related recommendations to the Fourth Review Conference,<sup>54–56</sup> technical information and the references (expanded by more than 200 from those in the original SAB report<sup>44</sup>) provided herein (and in the ESI†) serve as a platform to help further clarify RCA-related technical aspects of obligations under the Convention.

The present article is a summation of the contributions of 37 authors, from across 30 nations, and serves to demonstrate how international scientific collaboration – science diplomacy<sup>2,20,23</sup> – can be facilitated through, and lend strong support to, an international disarmament treaty whose norms serve to promote a world in which chemistry is used only to achieve peace, progress and prosperity.

## Legal disclaimer

The views herein are those of the authors and do not necessarily reflect those of the OPCW, or any institutions affiliated with the co-authors. The authors, affiliated institutes, and OPCW bear no responsibility for the consequences of use of the 17 chemicals identified as fitting the RCA definition, and no responsibility for the misuse of the 43 chemicals that did not conform to the RCA definition, under the Convention. The chemicals described herein that are currently used for law enforcement purposes are not meant to be handled or used by the public.

## Conflicts of interest

The authors declare no conflicts of interest.

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## Notes and references

- 1 *Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction*, OPCW, The Hague, 1997.
- 2 J. E. Forman and C. M. Timperley, in *Responsible Conduct in Chemical Research and Practice: Global Perspectives*, ed. E. T. Contis, D. J. Phillips, A. A. Campbell, B. D. Miller and L. Brown, American Chemical Society Publication, Washington D.C., USA, 2018, ACS Symposium Series #1288, ch. 1, pp. 1–35.
- 3 OPCW public documents and downloadable resources, <https://www.opcw.org/> (accessed 1 November 2018).
- 4 OPCW science and technology resources, <https://www.opcw.org/special-sections/science-technology/science-technology-resources/> (accessed 22 September 2018).
- 5 2013 Nobel Peace Prize, <https://www.opcw.org/special-sections/nobel-peace-prize-2013/> (accessed 1 June 2018).
- 6 G. R. Hasegawa, *Villainous Compounds – Chemical Weapons & The American Civil War*, Southern Illinois University Press, Carbondale, Illinois, USA, 2015.
- 7 A. M. Prentiss, *Chemicals in War – A Treatise on Chemical Warfare*, McGraw-Hill Book Co., London, UK, 1937.
- 8 M. Freemantle, *The Chemist's War 1914–1918*, The Royal Society of Chemistry, Cambridge, UK, 2016.
- 9 E. J. Olajos and W. Stopford, *Riot Control Agents – Issues in Toxicology, Safety, and Health*, CRC Press, London, UK, 2004.
- 10 J. R. Walker, in *Britain and Disarmament - The UK and Nuclear, Biological and Chemical Weapons Arms Control and Programmes 1956–1975*, Routledge, Taylor and Francis, London, UK, 2012, ch. 4, pp. 31–48.
- 11 M. Crowley, *Chemical Control – Regulation of Incapacitating Chemical Agent Weapons, Riot Control Agents and their Means of Delivery*, Palgrave MacMillan, Basingstoke, UK, 2016.
- 12 L. Shang, M. Dando and M. Crowley, *Preventing Chemical Weapons: Arms Control and Disarmament as the Sciences Converge*, The Royal Society of Chemistry, Cambridge, UK, 2018.
- 13 M. Balali-Mood, R. Mathews, R. Pita, P. Rice, J. Romano, H. Thiermann and J. L. Willems, in *The Practical Guide for Medical Management of Chemical Warfare Casualties, Assistance and Protection Branch*, OPCW, 2016, pp. 108–116.
- 14 C. Green, F. B. Hopkins, C. D. Lindsay, J. R. Riches and C. M. Timperley, *Pure Appl. Chem.*, 2017, **89**, 231–248.
- 15 R. Black, C. M. Timperley and H. Kiljunen, in *Recommended Operating Procedures for Analysis in the Verification of Chemical Disarmament, The Blue Book 2017*, ed. P. S. Vanninen, VERIFIN, Finland, 2017, Section 1, Part A, ch. III, pp. 5–31.
- 16 OPCW guide to chemicals in Schedules of the Convention, [https://www.opcw.org/fileadmin/OPCW/Science\\_Technology/Guide\\_to\\_Schedules.pdf](https://www.opcw.org/fileadmin/OPCW/Science_Technology/Guide_to_Schedules.pdf) (accessed 1 June 2018).
- 17 SAB documents, <https://www.opcw.org/about-opcw/subsidiary-bodies/scientific-advisory-board/> (accessed 1 June 2018).



- 18 SAB fact sheet, [https://www.opcw.org/fileadmin/OPCW/Fact\\_Sheets/English/Fact\\_Sheet\\_11\\_-\\_SAB.pdf](https://www.opcw.org/fileadmin/OPCW/Fact_Sheets/English/Fact_Sheet_11_-_SAB.pdf), (accessed 1 June 2018).
- 19 A. G. Suárez, *OPCW Today* 3, 2014, pp. 6–7, [https://www.opcw.org/fileadmin/OPCW/OPCW\\_Today/OPCW\\_Today\\_-\\_Vol\\_3\\_No\\_1.pdf](https://www.opcw.org/fileadmin/OPCW/OPCW_Today/OPCW_Today_-_Vol_3_No_1.pdf), (accessed 1 June 2018).
- 20 B. Maneschi and J. E. Forman, *Science & Diplomacy*, 2015, 4(3), <http://www.sciencediplomacy.org/perspective/2015/intersection-science-and-chemical-disarmament>.
- 21 OPCW science advice, [https://www.opcw.org/fileadmin/OPCW/SAB/en/Science\\_Advice\\_at\\_OPCW\\_2018.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/Science_Advice_at_OPCW_2018.pdf), (accessed 22 September 2018).
- 22 P. Mahaffy, J. E. Forman, A. W. M. Hay and C. M. Timperley, *Chem. Int.*, 2016, **38**, 38–39.
- 23 J. E. Forman, C. M. Timperley, S. Sun and D. van Eerten, *Pure Appl. Chem.*, 2018, **90**, 1507–1525.
- 24 *Report of the Twentieth Session of the SAB*, SAB-20/1 of 14 June 2013, pp. 8–9, [www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-01\\_e\\_.pdf](http://www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-01_e_.pdf) (accessed 1 June 2018).
- 25 C. M. Timperley, J. E. Forman, M. Abdollahi, A. S. Al-Amri, I. P. Alonso, A. Baulig, V. Borrett, F. A. Cariño, C. Curty, D. González Berrutti, Z. Kovarik, R. Martínez-Álvarez, R. Mikulak, N. M. F. Mourão, R. Ponnadurai, S. Neffe, S. K. Raza, V. Rubaylo, K. Takeuchi, C. Tang, F. Trifirò, F. M. van Straten, P. S. Vanninen, V. Zaitsev, F. Waqar, M. S. Zina, M. M. Blum, H. Gregg, E. Fischer, S. Sun and P. Yang, *Talanta*, 2018, **188**, 808–832.
- 26 C. M. Timperley, J. E. Forman, M. Abdollahi, A. S. Al-Amri, I. P. Alonso, A. Baulig, V. Borrett, F. A. Cariño, C. Curty, D. Gonzalez, Z. Kovarik, R. Martínez-Álvarez, R. Mikulak, N. M. F. Mourão, P. Ramasami, S. Neffe, S. K. Raza, V. Rubaylo, K. Takeuchi, C. Tang, F. Trifirò, F. M. van Straten, P. S. Vanninen, V. Zaitsev, F. Waqar, M. S. Zina, S. Holen and H. A. Weinstein, *Pure Appl. Chem.*, 2018, **90**, 1647–1670.
- 27 C. M. Timperley, J. E. Forman, M. Abdollahi, A. S. Al-Amri, A. Baulig, D. Benachour, V. Borrett, F. A. Cariño, M. Geist, D. Gonzalez, W. Kane, Z. Kovarik, R. Martínez-Álvarez, N. M. F. Mourão, S. Neffe, S. K. Raza, V. Rubaylo, A. G. Suárez, K. Takeuchi, C. Tang, F. Trifirò, F. M. van Straten, P. S. Vanninen, S. Vučinić, V. Zaitsev, M. Zafar-Uz-Zaman, M. S. Zina and S. Holen, *Toxicology*, submitted.
- 28 C. M. Timperley, J. E. Forman, M. Abdollahi, A. S. Al-Amri, A. Baulig, D. Benachour, V. Borrett, F. A. Cariño, M. Geist, D. Gonzalez, W. Kane, Z. Kovarik, R. Martínez-Álvarez, N. M. F. Mourão, S. Neffe, S. K. Raza, V. Rubaylo, A. G. Suárez, K. Takeuchi, C. Tang, F. Trifirò, F. M. van Straten, P. S. Vanninen, S. Vučinić, V. Zaitsev, M. Zafar-Uz-Zaman, M. S. Zina, S. Holen, W. S. Alwan and V. Suri, *Toxicology*, DOI: 10.1016/j.tox.2018.11.009.
- 29 M. C. Cesa, V. F. Ferreira, J. E. Forman, C. Tang, C. M. Timperley, C. Tran and B. West, *Pure Appl. Chem.*, 2018, **90**, 1501–1506.
- 30 J. E. Forman, C. M. Timperley, P. Aas, M. Abdollahi, I. P. Alonso, A. Baulig, R. Becker-Arnold, V. Borrett, F. A. Cariño, C. Curty, D. Gonzalez, Z. Kovarik, R. Martínez-Álvarez, R. Mikulak, E. S. Nogueira, P. Ramasami, S. K. Raza, A. E. M. Saeed, K. Takeuchi, C. Tang, F. Trifirò, F. M. van Straten, F. Waqar, V. Zaitsev, M. S. Zina, K. Grolmusová, G. Valente, M. Payva, S. Sun, A. Yang and D. van Eerten, *Pure Appl. Chem.*, 2018, **90**, 1527–1557.
- 31 *The Himsworth Report Part II: Report of the Enquiry into the Medical and Toxicological Aspects of CS; Use of Chemical Agents for Internal Security Operations; Possible Carcinogenicity of CS*, DEFE 24/1911, National Archives, Kew, London, UK, 1 January 1971–31 December 1977.
- 32 *Report of Fourth Session of the Scientific Advisory Board*, SAB-IV/1 of 6 February 2001, pp. 14–16 and p. 22, [www.opcw.org/fileadmin/OPCW/SAB/en/SABIV1\\_e\\_.pdf](http://www.opcw.org/fileadmin/OPCW/SAB/en/SABIV1_e_.pdf), (accessed 1 June 2018).
- 33 *Report of the Second Session of the Scientific Advisory Board*, SAB-II/1 of 23 April 1999, [www.opcw.org/fileadmin/OPCW/SAB/en/SABII1\\_e\\_.pdf](http://www.opcw.org/fileadmin/OPCW/SAB/en/SABII1_e_.pdf), (accessed 1 June 2018).
- 34 *Report of the Third Session of the Scientific Advisory Board*, SAB-III/1 of 27 April 2000, pp. 2–3, [www.opcw.org/fileadmin/OPCW/SAB/en/sab-iii-01.pdf](http://www.opcw.org/fileadmin/OPCW/SAB/en/sab-iii-01.pdf), (accessed 1 June 2018).
- 35 C. Rothenberg, S. Achanta, E. R. Svendsen and S. E. Jordt, *Ann. N. Y. Acad. Sci.*, 2016, **1378**, 96–107.
- 36 B. Bröne, P. J. Peeters, R. Marrannes, M. Mercken, R. Nuydens, T. Meert and H. J. M. Gijzen, *Toxicol. Appl. Pharmacol.*, 2008, **231**, 150–156.
- 37 B. F. Bessac, M. Sivula, C. A. von Hehn, A. I. Caceres, J. Escalera and S. E. Jordt, *FASEB J.*, 2009, **23**, 1102–1114.
- 38 H. J. M. Gijzen, D. Berthelot, M. Zaja, B. Bröne, I. Geuens and M. Mercken, *J. Med. Chem.*, 2010, **53**, 7011–7020.
- 39 C. D. Lindsay, C. Green, M. Bird, J. T. A. Jones, J. R. Riches, K. K. McKee, M. S. Sandford, D. A. Wakefield and C. M. Timperley, *R. Soc. Open Sci.*, 2015, **2**, 140160.
- 40 C. E. Paulsen, J. P. Armanche, Y. Gao, Y. Cheng and D. Julius, *Nature*, 2015, **520**, 511–517.
- 41 M. J. Caterina, M. A. Schumacher, M. Tominaga, T. A. Rosen, J. D. Levine and D. Julius, *Nature*, 1997, **389**, 816–824.
- 42 L. Darré and C. Domene, *Mol. Pharm.*, 2015, **12**, 4454–4465.
- 43 S. M. Hanson, S. Newstead, K. J. Swartz and M. S. P. Sansom, *Biophys. J.*, 2015, **108**, 1425–1434.
- 44 *Response to the Director-General's request to the SAB to provide consideration on which riot control agents are subject to declaration under the Convention*, OPCW SAB Twenty-Fifth Session from 27–31 March 2018, SAB-25/WP.1 of 27 March 2017, [https://www.opcw.org/fileadmin/OPCW/SAB/en/sab25wp01\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/sab25wp01_e_.pdf), (accessed 17 June 2018).
- 45 *Declaration of riot control agents: advice from the SAB*, OPCW Technical Secretariat, S/1177/2014 of 1 May 2014, [https://www.opcw.org/fileadmin/OPCW/S\\_series/2014/en/s-1177-2014\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/S_series/2014/en/s-1177-2014_e_.pdf), (accessed 17 June 2018).
- 46 *Report of SAB at its Twenty-Fifth Session from 27–31 March 2017*, SAB-25/1\* of 31 March 2017, paras. 11.1–11.2, [https://www.opcw.org/fileadmin/OPCW/SAB/en/sab2501\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/sab2501_e_.pdf) (accessed 17 June 2018).
- 47 *SAB poster on definition of a riot control agent*, [https://www.opcw.org/fileadmin/OPCW/Science\\_Technology/riot\\_control\\_agents\\_poster.pdf](https://www.opcw.org/fileadmin/OPCW/Science_Technology/riot_control_agents_poster.pdf), (accessed 17 June 2018).



- 48 *Note by the Director-General, Eighty-Fifth Session from 11-14 July 2017, EC-85/DG.8* of 1 May 2017, para. 18, [https://www.opcw.org/fileadmin/OPCW/SAB/en/ec85dg08\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/ec85dg08_e_.pdf) (accessed 22 September 2018).
- 49 C. M. Timperley, *Lecture to States Parties to the Chemical Weapons Convention*, OPCW Headquarters, 8 March 2017, [https://www.opcw.org/fileadmin/OPCW/Science\\_Technology/Diplomats\\_Programme/20170308\\_Science\\_For\\_Diplomats\\_RCA\\_CTimperley.pdf](https://www.opcw.org/fileadmin/OPCW/Science_Technology/Diplomats_Programme/20170308_Science_For_Diplomats_RCA_CTimperley.pdf) (accessed 1 June 2018).
- 50 R. J. Mathews, *Pure Appl. Chem.*, 2018, **90**, 1559–1575.
- 51 *Report of Fifteenth Session of the SAB from 12-14 April 2010, SAB-15/1* of 14 April 2010, paras. 13.1–13.3, [https://www.opcw.org/fileadmin/OPCW/SAB/en/sab-15-01\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/sab-15-01_e_.pdf) (accessed 17 June 2018).
- 52 C. M. Timperley, *Address to the States Parties of the Chemical Weapons Convention during a side-event at the Twenty-Second Session of the Conference of the States Parties*, 28 November 2017, [https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB\\_Chair\\_Presentation\\_at\\_CSP22\\_Side\\_Event\\_on\\_CNS-Acting\\_Chemicals.PDF](https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB_Chair_Presentation_at_CSP22_Side_Event_on_CNS-Acting_Chemicals.PDF) (accessed 22 September 2018).
- 53 *Fact sheet on considerations on CNS Acting Chemicals by the SAB since entry-into-force of the Chemical Weapons Convention, Twenty-Second Session of Conference of States Parties*, 28 November 2017, [https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB\\_Considerations\\_on\\_CNS-Acting\\_Chemicals\\_2003-2017.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB_Considerations_on_CNS-Acting_Chemicals_2003-2017.pdf), (accessed 22 September 2018).
- 54 *Report of the SAB 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, 21-30 November 2018, RC-4/DG.1* of 30 April 2018, [https://www.opcw.org/fileadmin/OPCW/CSP/RC-4/en/rc4dg01\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/CSP/RC-4/en/rc4dg01_e_.pdf) (accessed 7 September 2018).
- 55 *Quick reference guide to recommendations of the OPCW SAB's report on developments in science and technology to the Fourth Review Conference, RC-4/DG.1*, 30 April 2018, [https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB\\_RC4-Executive\\_Summary\\_Recommendations\\_-\\_web.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/SAB_RC4-Executive_Summary_Recommendations_-_web.pdf) (accessed 22 September 2018).
- 56 J. E. Forman, *Presentation to the chemical industry*, 9 July 2018, [https://www.opcw.org/fileadmin/OPCW/SAB/en/20180709\\_SAB\\_Recommendation\\_Briefing\\_Industry\\_Cluster.pdf](https://www.opcw.org/fileadmin/OPCW/SAB/en/20180709_SAB_Recommendation_Briefing_Industry_Cluster.pdf) (accessed 22 September 2018).
- 57 C. M. Timperley, in *Fluorine Chemistry at the Millennium – Fascinated by Fluorine*, ed. R. E. Banks, Elsevier, Oxford, UK, 2000, ch. 29, pp. 499–537.
- 58 C. M. Timperley and J. Tattersall, in *Best Synthetic Methods: Organophosphorus (V) Chemistry*, ed. C. M. Timperley, Elsevier, Oxford, UK, 2015, ch. 1.10, pp. 33–62.
- 59 H. Rice, C. H. Dalton, M. E. Price, S. J. Graham, A. C. Green, J. Jenner, H. J. Groombridge and C. M. Timperley, *Proc. R. Soc. London, Ser. A*, 2015, **471**, 20140891.
- 60 J. R. Riches, R. W. Read, R. M. Black, N. J. Cooper and C. M. Timperley, *J. Anal. Toxicol.*, 2012, **36**, 647–656.
- 61 C. D. Lindsay, J. R. Riches, N. Roughley and C. M. Timperley, in *Issues in Toxicology, Chemical Warfare Toxicology, Volume 2: Management of Poisoning*, ed. F. Worek, J. Jenner and H. Thiermann, The Royal Society of Chemistry, Cambridge, UK, 2016, ch. 8, pp. 259–313.
- 62 M. Halme, Various mass spectrometric methods for the screening and identification of metabolites of toxic and incapacitating chemicals, Academic Dissertation, University of Helsinki, Helsinki, Finland, 2015.
- 63 T. Köli, P. S. Vanninen, C. M. Timperley, J. R. Riches and N. Roughley, in *Recommended Operating Procedures for Analysis in the Verification of Chemical Disarmament, The Blue Book 2017*, ed. P. S. Vanninen, VERIFIN, Finland, 2017, Section 3, Part F, ch. IX, pp. 651–672.
- 64 J. F. Casale, J. R. Mallett and E. M. Guest, *Forensic Chem.*, 2017, **3**, 74–80.
- 65 *Joint paper on the aerosolisation of central nervous system-acting chemicals for law enforcement purposes, OPCW Conference of the States Parties, Twenty-Second Session from 27 November - 1 December 2017, C-22/NAT.5* of 28 November 2017, <https://csp22.opcw.org/documents/> (accessed 22 September 2018).
- 66 J. S. Ketchum, *Chemical Warfare Almost Forgotten – A Personal Story of Medical Testing of Army Volunteers with Incapacitating Chemical Agents during the Cold War (1955-1975)*, ChemBooks Inc., Santa Rosa, California, USA, 2006.
- 67 B. C. Garrett and J. Hart, in *The Historical Dictionary of Nuclear, Biological, and Chemical Warfare; Historical Dictionaries of War, Revolution and Civil Unrest*, No. 33, The Scarecrow Press Inc., Plymouth, UK, 2007, p. 44.
- 68 *Response by the Director-General to the report of the SAB on Developments in Science and Technology for the Fourth Special Session of the Conference of States Parties to Review the Operation of the Chemical Weapons Convention, Fourth Session from 19-30 November 2018, RC-4/DG.2* of 1 June 2018, paras. 22–23, [https://www.opcw.org/fileadmin/OPCW/CSP/RC-4/en/rc4dg02\\_e\\_.pdf](https://www.opcw.org/fileadmin/OPCW/CSP/RC-4/en/rc4dg02_e_.pdf) (22 September 2018).

