Conference paper

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Advice from the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons on isotopically labelled chemicals and stereoisomers in relation to the Chemical Weapons Convention

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Abstract: The Chemical Weapons Convention (CWC) is an international disarmament treaty that prohibits the development, stockpiling and use of chemical weapons. This treaty has 193 States Parties (nations for which the treaty is binding) and entered into force in 1997. The CWC contains schedules of chemicals that have been associated with chemical warfare programmes. These scheduled chemicals must be declared by the States that possess them and are subject to verification by the Organisation for the Prohibition of Chemical Weapons (OPCW, the implementing body of the CWC). Isotopically labelled and stereoisomeric variants of the scheduled chemicals have presented ambiguities for interpretation of the requirements of treaty implementation, and advice was sought from the OPCW's Scientific Advisory Board (SAB) in 2016. The SAB recommended that isotopically labelled compounds or stereoisomers related to the parent compound specified in a schedule should be interpreted as belonging to the same schedule. This advice should benefit scientists and diplomats from the CWC's State Parties to help ensure a consistent approach to their declarations of scheduled chemicals (which in turn supports both the correctness and completeness of declarations under the CWC). Herein, isotopically labelled and stereoisomeric variants of CWC-scheduled chemicals are reviewed, and the impact of the SAB advice in influencing a change to national licensing in one of the State Parties is discussed. This outcome, an update to national licensing governing compliance to an international treaty, serves as an example of the effectiveness of science diplomacy within an international disarmament treaty.

Keywords: Annex on Chemicals; BZ; chemical warfare agent; Chemical Weapons Convention 2017; diastereomer; enantiomer; isotope; isotopically labelled; National Authority; nitrogen mustard; Organisation for the Prohibition of Chemical Weapons (OPCW); organophosphorus nerve agent; sarin; scheduled chemical; science diplomacy; science policy; stereoisomer; sulfur mustard; vesicant.

Introduction

The Chemical Weapons Convention (CWC or hereinafter "the Convention") is an international disarmament treaty banning chemical weapons. The nations (States) party to the treaty are required to destroy any chemical weapon stockpiles and production facilities that they possess and to implement national laws that provide oversight for certain chemicals considered to be relevant to the intent and purpose of the treaty [1]. It is the first disarmament treaty to introduce a verifiable ban on an entire class of weapons of mass destruction. The Convention entered into force on 29 April 1997 and today includes 193 States Parties. This leaves four States outside its obligations: the Democratic People's Republic of Korea, Egypt, Israel, and South Sudan.

The Convention is implemented by the Organisation for the Prohibition of Chemical Weapons (OPCW) which has its headquarters in The Hague, the Netherlands.[1] The OPCW is an international organisation outside the United Nations system and was awarded the Nobel Peace Prize in 2013 for 'its extensive efforts to eliminate chemical weapons' [2]. It fulfils the object and purpose of the Convention and at the beginning of 2018 had verified the destruction of over 96 % of the world's declared stockpile of 72 304 metric tonnes of chemical agents [3]. Treaty implementation is supported through evidence-based scientific advice from an independent Scientific Advisory Board (SAB), which serves as input for decision-making by the Director-General and the States Parties. The SAB represents a scientific advisory mechanism for the provision of science advice to support policy making (as opposed to providing advice on policy for science).

1 All States Parties of the Convention are automatically members of the OPCW. The OPCW comprises three principal organs: the Conference of the States Parties, the Executive Council, and the Technical Secretariat. The Conference of the States Parties oversees the implementation of the Convention, promotes the objectives of the treaty, and reviews compliance with it. The Conference is composed of representatives of all member nations of the OPCW, each of which has one vote. Ordinarily it meets annually for one week in The Hague. Special sessions of the Conference can be convened when decided by the Conference, or when requested by the Executive Council or one third of all States Parties. In 2003, 2008 and 2013 and at five-yearly intervals thereafter, the Conference has convened special sessions to review the operation of the Convention (the so-called "Review Conferences"). The Conference may also meet to consider proposed amendments to the Convention.

The Convention defines chemical weapons through its Article II as:

(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;*
(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 munitions and devices specified in subparagraph (b)* [1].

A "toxic chemical" is "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" [1].

A precursor is any chemical reactant which takes part at any stage in the production by whatever method of a chemical. This includes any key component of a binary or multicomponent chemical system. The "key component" is defined as "the precursor which plays the most important role in determining the toxic properties of the final product and reacts rapidly with other chemicals in the binary or multicomponent system" [1].

Certain toxic chemicals and precursors are subject to verification. They feature in Schedules 1, 2 and 3 in the Annex on Chemicals to the Convention (given in Appendix 1 herein) [4, 5]. The schedules are based mainly on chemicals associated with historical chemical warfare programmes and use, although some toxic chemicals used in the First World War, considered obsolete during the negotiations of the Convention, were excluded.[2] The schedules contain specific chemicals along with families intended to encompass analogues with known or predicted properties similar to those of chemical warfare agents (CWAs) that could pose a risk to the Convention. While a mechanism exists for States Parties to amend the schedules, no proposals for adding new chemicals have been formally put forward since the Convention entered into force, although suggestions by States Parties may soon be forthcoming.[3]

Most of the toxic chemicals and precursors in the schedules relate to three classes of nerve agents (G agents, tabun and analogues, and V agents) and three classes of vesicant (sulfur mustards, Lewisites, and nitrogen mustards) [6]. With the exception of tabun and the nitrogen mustards, these agents accounted for most of the stockpile of toxic chemicals declared worldwide [7]. Other toxic chemicals in the schedules are saxitoxin (a natural product formed by cyanobacteria that is responsible for causing paralytic shellfish poisoning), ricin (a protein toxin found in the castor bean), the central nervous system (CNS) acting chemical 3-quinuclidinyl benzilate (BZ) [8], the organophosphorus pesticide amiton [9], plus toxic industrial chemicals (which include phosgene and hydrogen cyanide), some having been used historically as CWAs. The precursors are based on the known primary production routes to Schedule 1 or Schedule 2 chemicals; however, they do not necessarily cover all the possible synthetic routes. Some chemicals on the schedules can exist as enantiomers and/or diastereomers, but the schedules do not distinguish among these.

The States Parties to the Convention are obligated to: (a) disarm chemically by destroying all stockpiles of chemical weapons, facilities that produced them, and any old or abandoned chemical weapons;[2] (b) never

2 Some historically used chemical weapons were considered obsolete when the text of the Convention was finalised. Their chemical content is often excluded from the schedules, e.g. chlorine (Cl_2, which is also an important high-volume industrial chemical), diphenyl cyanoarsine (Ph_2AsCN) or diphenyl chloroarsine (Ph_2AsCl). It is still the case that weaponised forms of these chemicals are unearthed and must be disposed of. For purposes of treaty implementation, old chemical weapons (OCW) are often considered to be chemical weapons produced before 1925, or between 1925 and 1946, which have deteriorated sufficiently to prevent their use as chemical weapons.

3 Any State Party may propose amendments to the Convention under its Article XV and this includes to the Annex on Chemicals. The proposed amendment shall be considered by an Amendment Conference involving the States Parties. In light of recent events involving unscheduled nerve agents (specifically the "Salisbury Incident" in March 2018 [70] and "Amesbury Incident" shortly thereafter), several States Parties have called for consideration of Schedule amendments [71].

to develop, produce, stockpile or use chemical weapons; (c) submit regular declarations to the OPCW on chemical production facilities meeting certain criteria relevant to the CWC within their territories, and on the production, processing, consumption, and import and export of scheduled chemicals; and (d) to allow the OPCW to carry out routine inspections on the territories of States Parties. Given these requirements, the ability to recognise whether a given chemical is subject to the provisions of the Convention is important for States Parties to maintain compliance [10].

This paper reproduces advice on isotopically labelled compounds and stereoisomers provided by the SAB to the Director-General on 28 April 2016 [11, 12], published here with additional background information for those interested in the better understanding of the nuances of how scientific input is brought into policy making. It is intended for a readership of chemists and other scientists with an interest in how science advice influences policy making. A scientific analysis of the relationships between isotopically labelled and stereoisomeric chemicals and those specified in the schedules is provided; and the recommendations by the SAB on how chemicals relevant to Schedules 1, 2 and 3 should be considered in relation to the Convention are given. The paper closes with an example of how the SAB's advice influenced a change to national licensing of one State Party. We thus provide a case study on how science advice can be used within an international disarmament treaty to strengthen further the objectives of the CWC. We finish by describing future prospects for the advice given in relation to the implementation of the Convention. This paper is the second in a series of scientific publications produced by the SAB this year [13]. These publications represent contributions of scientists from across 25 nations, a demonstration of how international scientific collaboration ("science diplomacy") can be facilitated through, and lend support to, an international disarmament treaty.

Isotopically labelled chemicals and stereoisomers

To meet obligations under the Convention, and ensure complete and accurate declarations by States Parties – Parts VI, VII and VIII to the CWC's Annex on Implementation and Verification require that chemicals falling under Schedules 1, 2, and 3 must be clearly identifiable [1]. Some isotopically labelled Schedule 1 and Schedule 2 chemicals, and Schedule 2 chemicals that could exist as distinct stereoisomers (e.g. the stereoisomers of BZ), had presented ambiguity as to how they should be declared [14].

The Convention's Annex on Chemicals identifies chemicals through a combination of chemical families and/or specific chemical names accompanied by a corresponding Chemical Abstracts Service (CAS) registry number if one has been assigned [14]. The chemical name can be a common name or one standardised according to nomenclature rules established by the International Union of Pure and Applied Chemistry (IUPAC) [4] [15]. A CAS number is a unique numerical identifier assigned by the CAS to every chemical substance described in the scientific (or patent) literature from 1957 to today[5] [16]. As a CAS number is only assigned if a chemical has appeared in a publication where it was produced or discovered, isotopically labelled scheduled chemicals and stereoisomers of scheduled chemicals prepared, but not published in the scientific literature, will not have had a CAS number assigned to them (the same applies for any chemical whose molecular structure would fall under the Schedules but has not been published in the scientific or patent literature).

4 IUPAC has a long-standing partnership with OPCW, which was cemented further when the OPCW Director-General, Ambassador Ahmet Üzümcü, and the President of IUPAC, Professor Natalia Tarasova, signed a Memorandum of Understanding (MoU) on 1 December 2016. This pledged to enhance cooperation to keep abreast of developments in chemistry, responsibility and ethics in science, and education and outreach [72].

5 The chemical registry system was developed by the Chemical Abstracts Service (CAS) from work that started in the early 1960s after perfection of an algorithm for generating a unique and unambiguous computer language representation of the molecular configuration of each chemical. Since January 1965, the structures, names, and molecular formulas of all substances indexed for chemical abstracts have been recorded in computer files that constitute the Chemical Registry System. Each substance is assigned a permanent computer checkable registry number that identifies it in the CAS database and links it to the structure record, the names used for the chemical in the literature, and its Chemical Abstracts index name.

CAS numbers are intended to provide a unique, unmistakable identifier for chemicals. However, a chemical will have different CAS numbers assigned to analogues containing isotopic labels. A stereoisomer will also have a different CAS number from that of an isomeric mixture (whether racemic, scalemic, or comprising other stereoisomers, e.g. epimers or diastereomers). The following examples illustrate the ambiguity that could arise [14]:

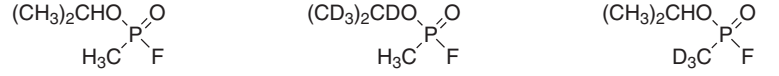
(a) The nitrogen mustard bis(2-chloroethyl)methylamine (**1**) (HN2) is listed in Schedule 1.A.06 with CAS registry number 51-75-2. The ^{14}C-isotopically labelled molecule, bis(2-chloroethyl)methyl[^{14}C]amine (**2**), has not been assigned a CAS registry number. If only the exact name and/or CAS number listed in Schedule 1.A.06 were considered for verification purposes, the ^{14}C-labelled nitrogen mustard might not be identified as a scheduled chemical (see the structures in Fig. 1).

(b) Another example involves three isotopic variations of sarin (Fig. 2): isopropyl methylphosphonofluoridate (**3**), isopropyl-d_7 methylphosphonofluoridate (**4**), and isopropyl methyl-d_3-phosphonofluoridate (**5**). The first of these is sarin, as listed in Schedule 1.A.01 (with CAS number 107-44-8). The other two are deuterated analogues of sarin. It has been argued that compound **4** should be considered under Schedule 2.B.04 (Precursors: chemicals except for those listed under Schedule 1, containing a phosphorus atom to which is bonded one methyl, ethyl or propyl (normal or iso) group but not further carbon atoms) rather than Schedule 1.A.01 (to which sarin belongs). It has also been argued that analogue **5** should not be considered under any CWC schedule because the "methyl" (of methyl, ethyl, propyl and isopropyl) specified in Schedule 1.A.01 or Schedule 2.B.04 corresponds to "CH_3" only, and not to any deuterated or otherwise isotopically labelled version.

(c) BZ highlights the ambiguity for stereoisomers. BZ is listed in Schedule 2.A.03, alongside its chemical name and CAS number 6581-06-2; yet its structure is not shown. BZ can exist as two enantiomers, which have been assigned CAS numbers 62869-69-6 (*R*-(–)-enantiomer) and 62869-68-5 (*S*-(+)-enantiomer) (Fig. 3). If only the exact name and/or CAS number listed in Schedule 2.A.03 were considered, stereoisomers might not be identified as scheduled chemicals.

Bis(2-chloroethyl)methylamine (**1**) Bis(2-chloroethyl)methyl[^{14}C]amine (**2**)

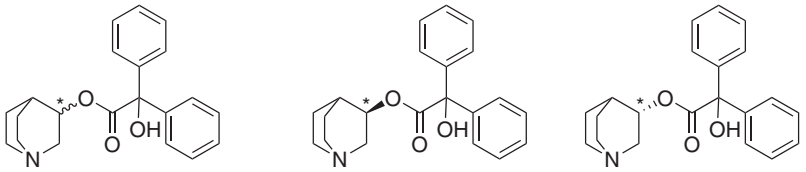
Fig. 1: Nitrogen mustard HN2 (*left*) and a ^{14}C-labelled analogue (*right*).



(**3**) (**4**) (**5**)

Isopropyl methylphosphonofluoridate | Isopropyl-d_7 methylphosphonofluoridate | Isopropyl methyl-d_3-phosphonofluoridate

Fig. 2: Sarin (*left*) and two deuterated analogues (*middle and right*).



3-Quinuclidinyl benzilate (BZ) CAS 6581-06-2 Schedule 2.A.03 | (*R*)-(–)-BZ CAS 62869-69-6 | (*S*)-(+)-BZ CAS 62869-68-5

Fig. 3: Racemic BZ (*left*) and its enantiomers (*middle and right*). The asymmetric carbon atom is marked with an asterisk.

The OPCW Director-General's request

To resolve the ambiguities, the OPCW Director-General requested advice from the SAB[6] [14]. The SAB consists of 25 members (Fig. 4) appointed by the Director-General from nominees submitted by States Parties [17–20]. The members are selected on the strength of their expertise in scientific fields relevant to the implementation of the Convention and are from research organisations, chemical industry, defence, academia and/or military. Only citizens of States Parties are eligible to serve and do so in their individual capacity as independent experts. The term of office is 3 years and each member may serve for up to two consecutive terms. The Director-General makes the SAB's reports and his responses to these publically available [17]. This time the advice requested by the Director-General was to:

Fig. 4: The SAB with the Director-General at the Twenty-Third Session of the Board on 18 April 2016 [11]. The SAB endorsed the report containing the advice on isotopically labelled chemicals and stereoisomers then. From left to right: (Back Row) Professor Slawomir Neffe (Poland), Dr. Jonathan E. Forman (OPCW Technical Secretariat, Science Policy Adviser), Professor Zrinka Kovarik (Croatia), Professor Ponnadurai Ramasami (Mauritius), Dr. Koji Takeuchi (Japan), Professor Roberto Martínez-Álvarez (Spain), Dr Augustin Baulig (France), Dr Robert Mikulak (United States of America), Professor Volodymyr Zaitsev (Ukraine), Mr Francois Mauritz van Straten (South Africa), Dr Abdullah Saeed Al-Amri (Saudi Arabia), Dr Christophe Curty (Switzerland), Dr David Gonzalez (Uruguay), Professor Ferruccio Trifirò (Italy); (Front Row) Professor Isel Pascual Alonso (Cuba), Professor Mongia Said Zina (Tunisia), Ms Farhat Waqar (Pakistan), Professor Mohammad Abdollahi (Islamic Republic of Iran), Dr Christopher M. Timperley (United Kingdom, SAB Chair), His Excellency Ambassador Ahmet Üzümcü (OPCW Director-General), Mr Cheng Tang (China, SAB Vice-Chair), Dr Nicia Maria Fusaro Mourão (Brazil), Professor Paula Vanninen (Finland), Dr Veronica Borrett (Australia). The other SAB members – Dr Syed K. Raza (India), Professor Flerida Cariño (Philippines) and Mr Valentin Rubaylo (Russian Federation) – were unable to attend.

6 The existence of the SAB is mandated by the Convention (through its Article VIII). Its role is to enable the Director-General, in the performance of his functions, to render specialised advice to the States Parties in areas of science and technology relevant to the CWC. This role includes assessing and reporting to the Director-General developments in scientific and technological fields relevant to the Convention, and, as necessary, the provision of advice on proposed changes to the schedules that have been formulated by the States Parties.

- Provide technical recommendations on isotopic labelling of chemicals relevant to Schedule 1, 2 and 3 under the Convention;
- Assess whether the chemical properties of a chemical are altered, when subject to isotopic labelling, in a manner that would affect its relevance to the schedules of chemicals under the Convention; and
- Make technical recommendations on how stereoisomers of chemicals relevant to Schedules 1, 2 and 3 should be considered in relation to the Convention.

The Director-General noted that the SAB, in making its response, should recall previous advice from February 2008 [21] and October 2012 [22], which pointed out "there is not necessarily a one-to-one relationship between CAS registry numbers and chemical structures", and that CAS registry numbers should be considered not as absolute determinants of whether chemicals are included in the schedules, but as aids to identification.

The advice from the SAB

In response to the Director-General's request, the SAB provided two recommendations to the Director-General and States Parties (as stated in Ref. 12]). These are reproduced here:

Recommendation 1

The molecular parent structure of a chemical should determine whether it is covered by a schedule entry. This is because:

- It is inappropriate to rely upon CAS numbers to define chemicals covered by the schedules. Although relevant as aids to declaration and verification, CAS numbers should not be used as the means to identify a chemical, or to determine whether a chemical is included in, or excluded from, a schedule;
- Thus, if a chemical is included within a schedule, then all possible isotopically-labelled forms and stereoisomers of that chemical should be included, irrespective of whether or not they have been assigned a CAS number or have CAS numbers different to those shown in the Annex on Chemicals to the Convention. The isotopically labelled compound or stereoisomer related to the parent chemical specified in the schedule should be interpreted as belonging to the same schedule; and
- This advice is consistent with previous SAB views on this topic [21, 22].

Recommendation 2

Inclusion of appropriate analytical data in the OPCW Central Analytical Database (OCAD) for isotopically labelled relatives of scheduled compounds and stereoisomers, where available, is recommended.[7]

Findings

The evidence used to give the advice was gathered from the specialist knowledge of the SAB and the scientific literature. Information reviewed and conclusions drawn are described next.

7 The OCAD is a reference library of validated chromatographic, mass spectral and nuclear magnetic resonance (NMR) spectroscopic data of relevance to the Convention. It enables on-site analysis during OPCW inspections and continues to be regularly updated. It currently contains validated data for over 5000 scheduled chemicals and is the largest available library of analytical data for CWA-related compounds.

Isotopically labelled scheduled chemicals

Isotopic labelling is used to develop analytical methods for CWAs and precursors [23–29] and to study the mechanism of action of CWAs [30] and potential medical treatments [31]. The mechanism of action of CWAs is generally understood, although the precise mechanism of vesication by the sulfur and nitrogen mustards, and Lewisites 1 and 2 (Lewisite 3 is not vesicant), is yet to be elucidated, despite research over decades [32]. Isotope substitution is regarded as the smallest structural change in a molecule. Thus, isotopically labelled CWAs are presumably as hazardous as their unlabelled counterparts listed in the schedules.

The schedules of the Convention provide lists of chemicals that are subject to oversight, which would logically be applied to bulk samples of such chemicals (in small quantity for allowed uses of Schedule 1 chemicals and in large industrial-scale amounts for many of the Schedule 3 chemicals). Unless prepared in a way that enriches a certain isotope of an atom in the molecule, a given chemical does not exist solely as composites of these most abundant isotopes (e.g. ^{1}H, ^{12}C, ^{15}N, ^{16}O, ^{31}P). Rather, it exists as a mixture of molecules that contain different ratios of isotopes, and the ratios of each isotope will depend on its natural abundance. CAS numbers assigned to molecules that are not designated as enriched in a specific isotope of one or more of the atoms in the molecular structure, for regulatory purposes would be associated with samples containing natural abundances and ratios of the isotopes. A good example is the blister agent sulfur mustard – bis(2-chloroethyl)sulfide – in Schedule 1.A.04 with CAS number 505-60-2. This number is understood to refer to the structure containing the most abundant isotope of sulfur (^{32}S), which constitutes ~95 % of pure sulfur mustard. However, the sample will also contain ~5 % of sulfur mustard molecules containing other natural sulfur isotopes (^{33}S, ^{34}S, ^{35}S) (Fig. 5) [33]. ^{33}S- and ^{34}S-sulfur mustard have not been assigned CAS numbers (which is indicative of molecules enriched in these isotopes of sulfur never having had their preparation reported in the scientific literature). ^{35}S-Sulfur mustard has been isolated [34] and assigned CAS number 6755-76-6, which differs from the CAS number of sulfur mustard in Schedule 1.A.04. This could mean that in a control list that uses the CAS numbers specified in the schedules of the Convention as identifiers for chemicals, ^{35}S-sulfur mustard might not be identified for declaration, even though it is a minor constituent of the sulfur mustard identified in Schedule 1.A.04 by CAS number 505-60-2.

If the only chemicals considered to be covered by Schedule 1, for example, were those with CAS numbers listed in the Annex on Chemicals, then the deuterium (*d*)-labelled sulfur mustards [34–40] in Fig. 6 – all of which are likely to be as hazardous as the sulfur mustard in Schedule 1.A.04 under CAS 505-60-2 – might not be considered to be scheduled chemicals. This would seem unacceptable as isotopically labelled sulfur mustards could then be developed, produced and stockpiled, arguably legitimately, under the Convention. This would contravene the spirit of the Convention and removing such ambiguities would strengthen further its intent and purpose.

Furthermore, reliance on CAS numbers to identify scheduled chemicals would not address identification of mixtures of toxic chemicals for accurate declaration. For example, a mixture of 60:40 percent by

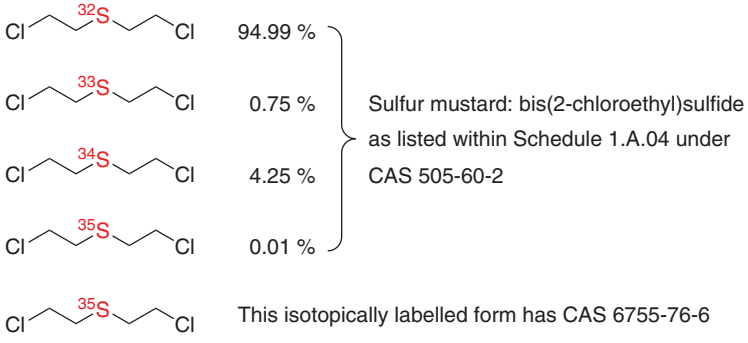


Fig. 5: Isotopically labelled sulfur mustards. Percentages of CAS 505-60-2 constituents were calculated from the natural abundances of isotopes of sulfur [33].

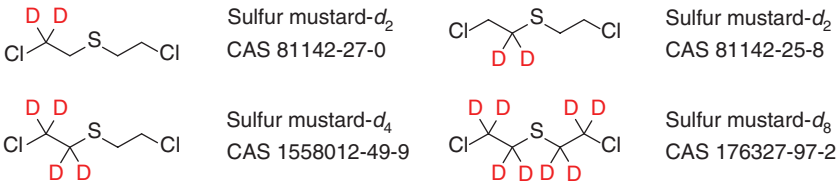


Fig. 6: Deuterated sulfur mustards. D denotes a deuterium atom in place of a hydrogen atom [34–40].

weight of sulfur mustard HD (Schedule 1.A.04, CAS 505-60-2) and O-mustard or T (Schedule 1.A.04, CAS 63918-89-8) was used to fill munitions in past chemical warfare programmes [41, 42]. This so-called HT mixture has a CAS number (Fig. 7a) that is absent from the schedules. Another example is a mixture of sulfur mustard (Schedule 1.A.04, CAS 505-60-2) and Lewisite 1 (L) (Schedule 1.A.05, CAS 541-25-3) which was also weaponised historically [43–46]. This mixture has a CAS number different from those CAS numbers of its pure components (Fig. 7b).

Another illustrative example is the route to sarin production from methylphosphonic dichloride [47, 48] through methylphosphonic difluoride [49] to sarin (Fig. 8). Isotopically labelled counterparts are shown underneath. All three have different CAS numbers to those present in the schedules for the unlabelled variants. Therefore they might not be identified as scheduled chemicals, yet sarin-d_3 is likely to be just as hazardous as sarin.

Schedule 1.A.01, containing sarin as a member of the *O*-alkyl alkylphosphonofluoridate family of chemicals, defines only structures with P-methyl, ethyl, and *n*- or *i*-propyl groups; these could be interpreted to comprise CH_3, C_2H_5, and C_3H_7 and not deuterated variants, for example CD_3, C_2D_5, and C_3D_7. This interpretation could be applied to all such scheduled chemicals. To someone well versed in chemistry, this may seem unlikely. However, it must be appreciated that the end users of the schedules may be regulatory bodies and not scientists. Thus, advice for these users would be that all isotopically labelled versions of scheduled chemicals should be considered to belong to the same schedule as the parent structure.

Capturing these isotopically labelled chemicals within the schedules requires acknowledging that they are identical for the purposes of declaration to their unlabelled counterparts already specified in the schedules.

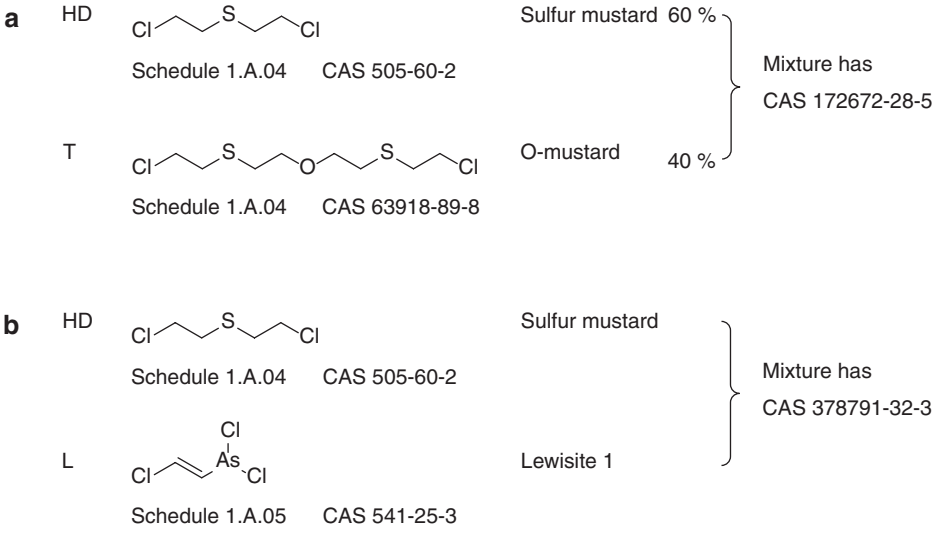


Fig. 7: (a) HD and T when pure have separate CAS numbers but a 60:40 mixture has been allocated a different CAS number. (b) HD and L when pure have separate CAS numbers but a mixture has been assigned a different CAS number.

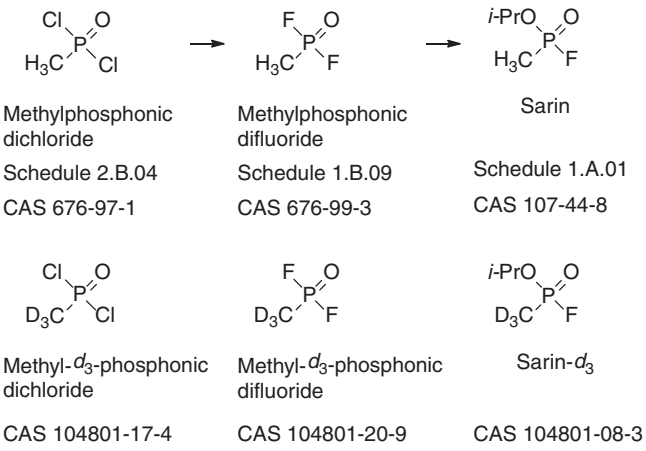


Fig. 8: Non-deuterated and deuterated precursors to sarin, and non-deuterated and deuterated sarin. All have different CAS numbers.

Stereoisomers of scheduled chemicals

Some toxic chemicals can exist as enantiomers (e.g. organophosphorus nerve agents) or diastereoisomers (e.g. the nerve agent soman) [50]. Nerve agent stereoisomers – enantiomers and/or diastereoisomers – show differences in biological activity (Table 1). The (+)-enantiomer is usually a weaker inhibitor of the enzyme acetylcholinesterase (AChE), whose inhibition disrupts the normal functioning of the nervous system, and less toxic than the (–)-enantiomer. The racemic mixture, a 1:1 molar ratio of each enantiomer, is denoted by the prefix (±) and has a biological activity from the sum contribution of the two enantiomers.

Standard synthetic pathways to CWAs are non-stereoselective and produce a racemic mixture of stereoisomers. Thus, one stereoisomer is naturally associated with the other, and should not be viewed independently of the other for the purposes of the schedules.

Table 1: Effect of nerve agent stereochemistry on the AChE inhibition rate constant and the acute lethality expressed as an LD_{50} value [47, 51–53].

Stereoisomer	Rate constant for AChE inhibition at 25 °C (M^{-1} min^{-1})[a]	LD_{50} mouse (μg kg^{-1})
(+)-tabun	4×10^5	837[b]
(–)-tabun	2×10^6	119[b]
(±)-tabun	NA	208[b]
(+)-sarin	$<3\times10^3$[d]	NA
(–)-sarin	1×10^7	41[b]
(±)-sarin	NA	83[b]
C(+)P(+)-soman	$<5\times10^3$	>5000[c]
C(–)P(+)-soman	$<5\times10^3$	>2000[c]
C(+)P(–)-soman	3×10^8	99[c]
C(–)P(–)-soman	2×10^8	38[c]
C(±)P(±)-soman	NA	156[c]
(+)-VX	2×10^6	165[b]
(–)-VX	4×10^8	13[b]
(±)-VX	NA	20[b]

LD_{50} is the lethal dose that kills half a group of test animals. [a]Rate constants for tabun and soman isomers were measured with electric eel AChE at pH 7.5 whereas those for sarin and VX enantiomers were obtained with bovine erythrocyte AChE. [b]Intravenous administration. [c]Subcutaneous administration. [d]Estimated from an experiment with optically enriched (+)-sarin (64 % enantiomeric excess). Note that the (–)-cyclosarin enantiomer, where the P-isopropyloxy group in sarin is replaced by a cyclohexyloxy group, inhibits AChE more strongly than (±)-cyclosarin and is the most toxic isomer [52], in line with the trend revealed in the table. NA denotes that the data were not available.

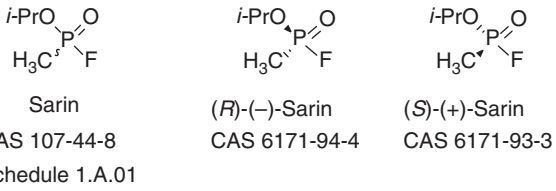


Fig. 9: Sarin and its two enantiomers have been assigned different CAS numbers.

Sarin listed in Schedule 1.A.01 and defined by CAS number 107-44-8 is understood to be a racemic mixture, comprising an approximately equal mixture of its enantiomers [54–58]. This mixture is denoted (±)-sarin. However, pure enantiomers have different CAS numbers: 6171-94-4 for the more toxic (*R*)-(–)-sarin and 6171-93-3 for the less toxic (*S*)-(+)-sarin (Fig. 9). As both are highly toxic and have similar properties to the (±)-material specified in Schedule 1.A.01, it would be inconsistent with the intent and purpose of the Convention to treat them differently from the racemic mixture.

Another example is provided by BZ [59]. It features in Schedule 2.A.03 under CAS number 6581-06-2. It can exist as enantiomers: (*R*)-(–)-BZ and (*S*)-(+)-BZ (however, producing this material under non-enantioselective conditions would produce a racemic mixture) (Fig. 3). Both enantiomers are capable of causing behavioural effects in humans (note that (*R*)-(–)-BZ is at least 20 times more potent than its (*S*)-(+)-stereoisomer in causing behavioural effects in dogs after subcutaneous administration [60]). Despite one enantiomer being more potent than the other, both can be used to affect life processes, and methods of production can potentially produce both enantiomers. For regulatory purposes the enantiomers of BZ would both fall under Schedule 2.A.03.

These examples are illustrative and more could be provided. However, the SAB did not find this necessary as the general concept was unchanged from example to example.

Conclusions

In its advice to the Director-General, the SAB concluded that isotopically labelled or stereoisomeric variants of scheduled chemicals should be interpreted as belonging to the schedule that includes the parent structure [12]. And that the structure of a chemical, regardless of its isotopic composition or spatial orientation of atoms, should determine whether that chemical falls within the schedules of the Convention. A principal reason for this was that the chemical functionality that makes the scheduled chemical toxic, or allows it to be a precursor to a toxic chemical, is still present in its isotopically labelled variants and different stereoisomers. Because of the very large number of isotopically labelled and stereoisomeric scheduled chemicals theoretically obtainable, it is inappropriate to rely solely on the CAS numbers specified in the schedules for identifying scheduled chemicals. The SAB also concluded that with the parent chemicals on the schedules, States Parties should treat isotopically labelled and stereoisomeric forms of such chemicals appropriately for declaration and verification purposes.

The importance of effective science-policymaker engagement [10, 61] was recognised in 2014 by the launch of an initiative within the OPCW entitled “Science for Diplomats”. This initiative institutionalised the holding of regularly scheduled lectures at OPCW Headquarters on scientific topics relevant to the Convention [62]. The advice provided to the Director-General by the SAB on isotopic labels, stereoisomers, and scheduled chemicals, was briefed to the States Parties in July 2016 at one of these events [63] to convey to diplomats the importance of the subject, and why nuances associated with molecular structures and CAS numbers, something that may seem abstract to their day to day considerations, were actually important for the implementation of the Convention (Fig. 10).

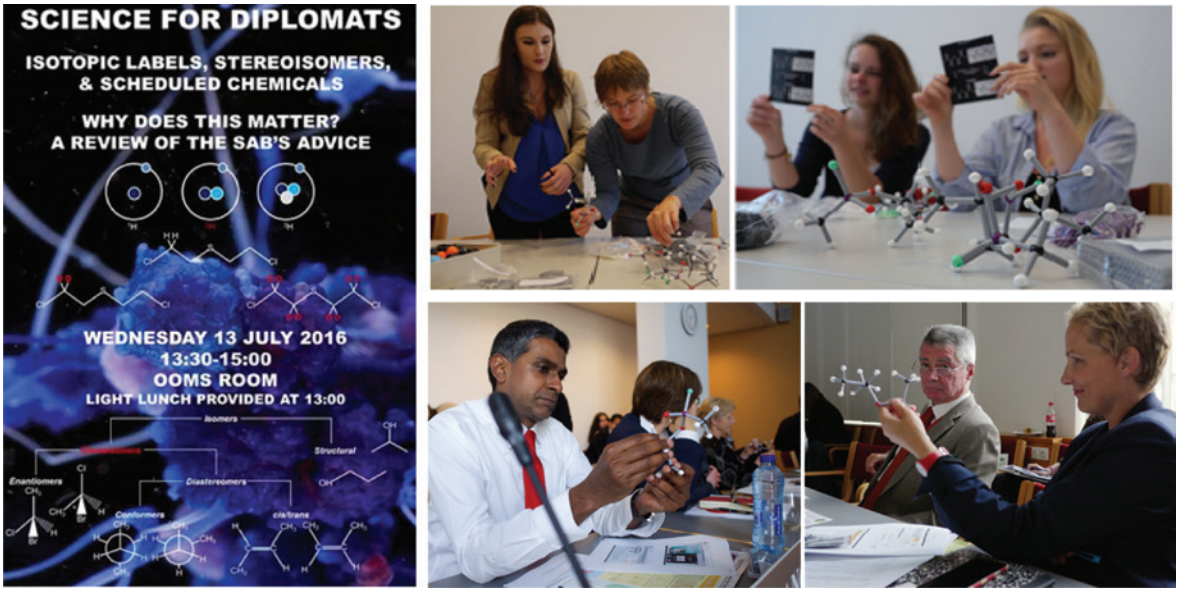


Fig. 10: Dr. Jonathan E. Forman, OPCW Science Policy Adviser and Secretary to the SAB, briefed the CWC States Parties on the SAB's advice on isotopic labels, stereoisomers, and scheduled chemicals, on 13 July 2016 at a "Science for Diplomats" event (*left*) during the Eighty-Second Session of the OPCW Executive Council [63]. Ball-and-stick molecular models prepared by OPCW interns (*top right*) were provided to diplomats (*bottom right*) who were taught to recognise the enantiomers of sarin to illustrate their relative spatial characteristics and non-superimposable nature, to understand that they are not the same molecules, and that both should be covered by Schedule 1 of the CWC, and declared as such.

Impact of the advice from the SAB: the change of UK legislation as an example

Teaching stereochemistry to government officials from 193 States charged with overseeing a disarmament treaty may seem like a distraction from the issues they might need to be focused on, yet this advice helped prompt a change to national licensing within a State Party of the Convention, namely the United Kingdom of Great Britain and Northern Ireland (the UK). In contextualising this outcome, we will start with a description of a National Authority (NA) to the Convention and the licensing policy adopted within its ambit.[8]

All States Parties are required to designate a NA to oversee implementation of the Convention and ensure its obligations are met.[9] The UK NA is based in the Department for Business, Energy & Industrial Strategy (BEIS) in

8 The work of a NA covers several areas including monitoring and reporting chemical activities, inspections of chemical industry sites, export and licensing controls, and national and international policy development. Preventing the non-proliferation of chemical weapons is fundamental to the Convention. Each State Party must ensure that toxic chemicals are only developed, produced, acquired, retained, transferred, or used for purposes that are not prohibited by the Convention. Anyone producing, processing, consuming, importing or exporting certain toxic chemicals is legally obligated to provide information about these activities to the NA, who declares this information to the OPCW annually.
To certify that all activities conform to the CWC, States Parties must subject facilities producing scheduled chemicals and facilities producing other chemicals that meet certain declarations criteria to inspection by the OPCW. This acts as a confidence-building measure that each State Party is meeting its obligations and acts as a deterrent against any contravention of the provisions of the Convention. It is a credit to the chemical industry worldwide that inspections are accomplished in a cooperative spirit which has helped demonstrate compliance.
The trade in certain chemicals covered by the Convention is controlled in a State Party through national export and import licensing regulations, operated by the NA and relevant national export control organisation(s). Anyone importing or exporting particular chemicals into or from the State Party must meet certain legal requirements, which may vary depending on the country supplying or receiving the chemicals. In some cases imports and exports are strictly prohibited, the types and quantities of chemicals limited, and a possession and use license from the NA required.
9 Internationally, NAs play an active and influential role in negotiations within the policymaking organs of the OPCW, providing representation at the OPCW Conference of the States Parties, Executive Council, and other meetings in The Hague.

London.[10] BEIS helps safeguard the peaceful applications of chemistry. It oversees implementation of the Convention in the UK, Crown Dependencies and Overseas Territories, in accordance with the provisions of the UK Chemical Weapons Act of 1996 [64]. This legislation places legal requirements on all entities (including companies, universities, transport and other bodies) and individuals that work with certain toxic chemicals within the UK.

Through the NA, the UK expanded in 2017 its licensing policy on chemicals that fall under Schedule 1 of the CWC [65] to include chemicals that were not specifically listed in Schedule 1 under a particular CAS number, but that shared a chemical structure with those that did. This approach was influenced by the SAB's advice, technical advice from scientific advisers at Dstl Porton Down, legal advice obtained nationally, and the results of a consultation exercise with UK stakeholders.

Fundamental to the objectives of the CWC, and the Schedule 1 licensing regime, are chemicals which can be (or have been) weaponised falling within its scope, and enabling NAs to tightly control possession and use of such chemicals. The UK NA wished to ensure that the licensing system was applied in a technically consistent way, so that chemicals with the same structures, names and toxic properties as chemicals explicitly listed in Schedule 1 were licensable, even if they had different CAS numbers. The UK now considers the molecular structure of a chemical to determine whether it is covered by Schedule 1. Therefore, isotopically labelled analogues, stereoisomers (both optical and geometric), and corresponding salts are licensable (Table 2). The inclusion of salts has significance as previous advice from the SAB recommended that salts of Schedule 1 chemicals should not be considered as non-scheduled chemicals [66], which may not always be the case under regulatory systems that strictly adhere to the exact text of the schedules of the Convention.

Table 2: Summary of which chemicals under each Schedule 1 section have been licensable since April 2017 in the UK: those that should be licensed are indicated by a cross [65].

Schedule	Isotopically labelled analogue	Corresponding salts	Stereoisomers
1.A.01 G agents	×		×
1.A.02 Tabun and analogues	×		×
1.A.03 V agents[a]	×	×	×
1.A.04 Sulfur mustards	×		
1.A.05 Lewisites	×		×
1.A.06 Nitrogen mustards	×	×	
1.A.07 Saxitoxin	×	×	×
1.A.08 Ricin	×		
1.B.09 Alkylphosphonyl difluorides (e.g. DF)	×		
1.B.10 O-Alkyl O-2-dialkylaminoethyl alkylphosphonites (e.g. QL)[a]	×	×	
1.B.11 Chlorosarin	×		×
1.B.12 Chlorosoman	×		×

[a]The CWC schedules for these chemicals include the corresponding protonated salts [1].

10 Full address of the UK NA: CWC UK National Authority, Department for Business, Energy and Industrial Strategy, 3rd Floor, 1 Victoria Street, London, SW1H 0ET. The NA has a CWC Advisory Committee to obtain advice from industrial and academic stakeholders on the implementation of the Convention and the UK Chemical Weapons Act, as well as on technical developments relevant to the Convention. The committee is currently chaired by Professor Alistair Hay OBE who won the OPCW-The Hague Award in 2015 [73].

To prevent over-burdensome and unnecessary licensing, to ensure human safety and support medical research, the UK NA implemented a number of limited exemptions [65]. These were necessary to avoid impeding the legitimate transfer, possession and/or use of, for example, paralytic shellfish poisoning diagnostic kits (which contain the Schedule 1 chemical saxitoxin) and some cancer treatments which can contain very small amounts of particular versions of Schedule 1 chemicals (for example, nitrogen mustard HN2), as well as contaminated items such as clothing and environmental samples which might contain traces of Schedule 1 chemicals. The changes to the UK's Schedule 1 licensing regime, including the exemptions, took effect from April 2017.

Outlook and future prospects

Every 5 years, the OPCW holds a Special Session of States Parties to review the operation of the Convention.[11] For this, the SAB prepares a report on developments in science and technology, for the OPCW Director-General and the States Parties.[12] The next such session – the Fourth Review Conference (RC-4) – will be held in November 2018.

Building on recommendation 1 herein (Section "Recommendation 1"), the SAB report to RC-4 advises against relying solely upon CAS numbers to define chemicals covered by the schedules: 'Although relevant as aids to declaration and verification, CAS numbers are not the only means to identify a chemical or determine whether a chemical is included in or excluded from a schedule' [66] The same report also advises that: 'To ensure the consistency of declarations, if a chemical is included within a schedule, then all possible isotopically-labelled forms and stereoisomers of that chemical should be included, irrespective of whether or not they have been assigned a CAS number or have CAS numbers different to those shown in the Annex on Chemicals of the Convention. The isotopically-labelled compound or stereoisomer related to the parent chemical specified in the schedule should be interpreted as belonging to the same schedule' [66].

Building on recommendation 2 herein (Section "Recommendation 2"), the SAB report to RC-4 states that: '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, toxins, and unscheduled chemicals that have been identified as posing a risk to the Convention' [66].

The SAB hopes that these recommendations will after due consideration by the States Parties, translate into policies that will help to make the world a safer place through strengthening the verification mechanism of the Convention, which has been instrumental to its success to date.

Acknowledgements: The SAB thanks Ambassador Ahmet Üzümcü for supporting the Board and providing its output to States Parties to inform their decision making. The SAB expresses its gratitude to Dr. Sarah Clapham, Dr. Jim McGilly and Mr. Matthew Brooks of Dstl, and to Mr. Terry Dance and Mr. Craig Wallbank of the UK National Authority in BEIS, for information and helpful feedback, especially on the change of licensing of scheduled chemicals in the UK. The SAB also acknowledges Ms. Marlene Payva, for her skillful assistance to the Board, the European Union for providing funding for activities of the Board, and the International Union of Pure and Applied Chemistry for its support during the run-up to RC-4 and the three Review Conferences held previously, to which it provided substantial scientific input [67–69].

11 The Convention stipulates that: 'The Conference shall not later than 1 year after the expiry of the fifth and tenth year after the entry into force of this Convention, and at such other times within that time period as may be decided upon, convene in special sessions to undertake reviews of the operation of this Convention. Such reviews shall take into account any relevant scientific and technological developments. At intervals of 5 years thereafter, unless otherwise decided upon, further sessions of the Conference shall be convened with the same objective' (CWC Article VIII, B. The Conference of the States Parties, paragraph 22 [1]).

12 One of the functions of the SAB is 'when directed by the Conference acting in accordance with paragraph 22 of Article VIII, provide advice and make recommendations taking into account any relevant scientific and technological developments for the purpose of assisting the Conference in its review of the Operation of the Convention' (Terms of Reference of the SAB, Rules of Procedure for the SAB and Temporary Working Groups of Scientific Experts, OPCW, June 2011, paragraph 2(f) [1]).

Appendix 1: The schedules of chemicals of the Chemical Weapons Convention.

Schedule 1

The following criteria shall be taken into account in considering whether a toxic chemical or precursor should be included in Schedule 1:

(a) It has been developed, produced, stockpiled or used as a chemical weapon as defined in Article II;

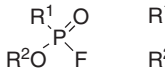
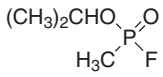
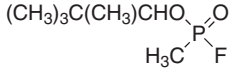
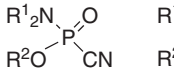
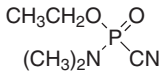
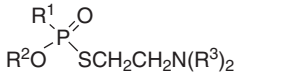
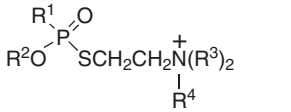
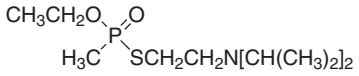
(b) It poses otherwise a high risk to the object and purpose of this Convention by virtue of its high potential for use in activities prohibited under this Convention because one or more of the following conditions are met:

(i) It possesses a chemical structure closely related to that of other toxic chemicals listed in Schedule 1, and has, or can be expected to have, comparable properties;

(ii) It possesses such lethal or incapacitating toxicity as well as other properties that would enable it to be used as a chemical weapon;

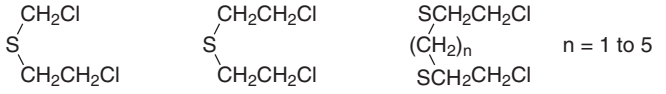
(iii) It may be used as a precursor in the final single technological stage of production of a toxic chemical listed in Schedule 1, regardless of whether this stage takes place in facilities, in munitions or elsewhere;

(c) It has little or no use for purposes not prohibited under this Convention

No.	Chemical/s	CAS number
A. Toxic chemicals		
Nerve agents		
1	O-Alkyl ($\leq C_{10}$, incl. cycloalkyl) alkyl (Me, Et, *n*-Pr or *i*-Pr)-phosphonofluoridates *Commonly known as G agents (but not GA)*  R^1 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) R^2 = C1-C10 (alkyl, cycloalkyl)	
	e.g. Sarin: *O*-Isopropyl methylphosphonofluoridate 	107-44-8
	Soman: *O*-Pinacolyl methylphosphonofluoridate 	96-64-0
2	O-Alkyl ($\leq C_{10}$, incl. cycloalkyl) N,N-dialkyl (Me, Et, *n*-Pr or *i*-Pr) phosphoramidocyanidates *Tabun (GA) and analogues*  R^1 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) R^2 = C1-C10 (alkyl, cycloalkyl)	
	e.g. Tabun: *O*-Ethyl *N*,*N*-dimethyl phosphoramidocyanidate 	77-81-6
3	O-Alkyl (H or $\leq C_{10}$, incl. cycloalkyl) *S*-2-dialkyl (Me, Et, *n*-Pr or *i*-Pr)-aminoethyl alkyl (Me, Et, *n*-Pr or *i*-Pr) phosphonothiolates *Commonly known as V agents*  R^2 = H or C1-C10 (alkyl, cycloalkyl) R^1 and R^3 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) and corresponding alkylated or protonated salts, e.g.  R^4 = H or unspecified alkyl	
	VX: *O*-Ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate  *Note! Schedule 1.A.03 includes partly hydrolysed V agents, as H is also included in the O-alkyl definition*	50782-69-9

Appendix 1 (continued)

No.	Chemical/s	CAS number
	Vesicants	
4	Sulfur mustards:	
	2-Chloroethylchloromethylsulfide	2625-76-5
	Mustard gas: bis(2-chloroethyl)sulfide	505-60-2
	Bis(2-chloroethylthio)methane	63869-13-6
	Sesquimustard: 1,2-bis(2-chloroethylthio)ethane	3563-36-8
	1,3-Bis(2-chloroethylthio)-*n*-propane	63905-10-2
	1,4-Bis(2-chloroethylthio)-*n*-butane	142868-93-7
	1,5-Bis(2-chloroethylthio)-*n*-pentane	142868-94-8
	Bis(2-chloroethylthiomethyl)ether	63918-90-1
	O-Mustard: bis(2-chloroethylthioethyl)ether	63918-89-8



Sulfur mustard e.g. sesquimustard Q, n = 2

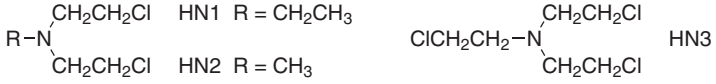
O-mustard (also known as T)

5	Lewisites	
	Lewisite 1: 2-chlorovinyldichloroarsine	541-25-3
	Lewisite 2: bis(2-chlorovinyl)chloroarsine	40334-69-8
	Lewisite 3: Tris(2-chlorovinyl)arsine	40334-70-1
	Lewisites 2 and 3 are impurities in Lewisite 1	

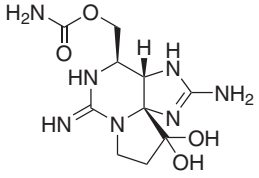
$ClCH{=}CHAsCl_2$ $(ClCH{=}CH)_2AsCl$ $(ClCH{=}CH)_3As$

Lewisite 1 Lewisite 2 Lewisite 3

6	Nitrogen mustards	
	HN1: bis(2-chloroethyl)ethylamine	538-07-8
	HN2: bis(2-chloroethyl)methylamine	51-75-2
	HN3: Tris(2-chloroethyl)amine	555-77-1
	Salts of nitrogen mustard are not included	

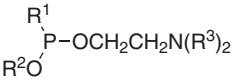
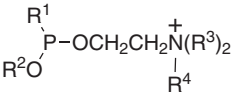
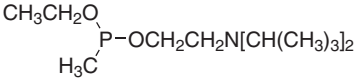
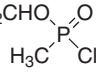
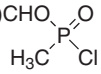


7	Saxitoxin	35523-89-8
	A marine toxin; salts or analogues are not included [74]	



8	Ricin	9009-86-3
	A heterogeneous glycoprotein extracted from the castor bean, approximate molecular mass of 65 kDa. The SAB recommended to the OPCW Director-General in 2009 the following definition be adopted for verification purposes:	
	'All forms of ricin originating from Ricinus communis, including any variations in the structure of the molecule arising from natural processes, or man-made modification designed to maintain or enhance toxicity, are to be considered ricin as long as they conform to the basic 'native' bipartite molecular structure of ricin that is required for mammalian toxicity, i.e. A and B chains linked only by a disulfide bond (A-S-S-B). Once the inter-chain S-S bond is broken or the protein denatured, it is no longer ricin' [75]	

Appendix 1 (continued)

No.	Chemical/s	CAS number
B. Precursors		
9	Alkyl (Me, Et, *n*-Pr or *i*-Pr) phosphonyl difluorides  R^1 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) e.g. DF: Methylphosphonyl difluoride *Also known as methylphosphonic difluoride* 	676-99-3
10	O-Alkyl (H or $\leq C_{10}$, incl. cycloalkyl) *O*-2-dialkyl (Me, Et, *n*-Pr or *i*-Pr)-aminoethyl alkyl (Me, Et, *n*-Pr or *i*-Pr) phosphonites  R^2 = H or C1-C10 (alkyl, cycloalkyl) R^1 and R^3 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) and corresponding alkylated or protonated salts  R^4 = H or unspecified alkyl e.g. QL: *O*-Ethyl *O*-2-diisopropylaminoethyl methylphosphonate 	57856-11-8
11	Chlorosarin: *O*-Isopropyl methylphosphonochloridate 	1445-76-7
12	Chlorosoman: *O*-Pinacolyl methylphosphonochloridate 	7040-57-5

Schedule 2

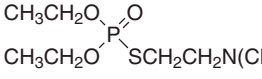
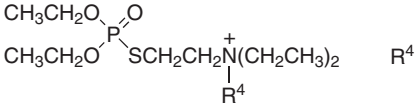
The following criteria shall be taken into account in considering whether a toxic chemical not listed in Schedule 1 or a precursor to a Schedule 1 chemical or to a chemical listed in Schedule 2, part A, should be included in Schedule 2:

(a) It poses a significant risk to the object and purpose of this Convention because it possesses such lethal or incapacitating toxicity as well as other properties that could enable it to be used as a chemical weapon;

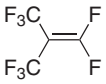
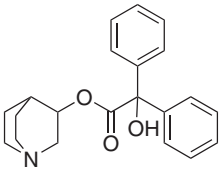
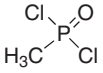
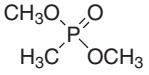
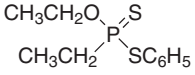
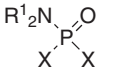
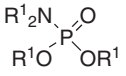
(b) It may be used as a precursor in one of the chemical reactions at the final stage of formation of a chemical listed in Schedule 1 or Schedule 2, part A;

(c) It poses a significant risk to the object and purpose of this Convention by virtue of its importance in the production of a chemical listed in Schedule 1 or Schedule 2, part A;

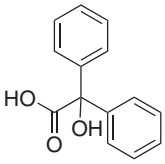
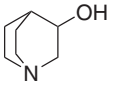
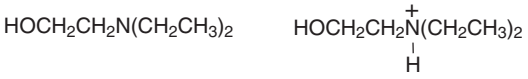
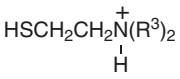
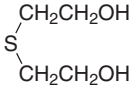
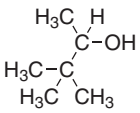
(d) It is not produced in large commercial quantities for purposes not prohibited under this Convention.

No.	Chemical/s	CAS number
A. Toxic chemicals		
1	Amiton: *O*,*O*-Diethyl *S*-[2-(diethylamino)ethyl] phosphorothiolate  and corresponding alkylated and protonated salts  R^4 = H or unspecified alkyl	78-53-5

Appendix 1 (continued)

No.	Chemical/s	CAS number
2	PFIB: 1,1,3,3,3-Pentafluoro-2-(trifluoromethyl)-1-propene *A toxic industrial by-product of fluoropolymer manufacture [76–80]* 	382-21-8
3	BZ: 3-Quinuclidinyl benzilate *A previously weaponized incapacitant/CNS-acting chemical* 	6581-06-2
B. Precursors		
4	Chemicals, except for those listed in Schedule 1, containing a phosphorus atom to which is bonded one methyl, ethyl or propyl (normal or iso) group but not further carbon atoms, e.g. Methylphosphonyl dichloride *Also known as methylphosphonic dichloride (DC)* 	676-97-1
	Dimethyl methylphosphonate 	756-79-6
	Exemption: Fonofos: *O*-Ethyl *S*-phenyl ethylphosphonothiolothionate *Commercial pesticide*  *Note! This schedule defines only one substituent (alkyl) on phosphorus and includes P(III) and P(V) chemicals; it therefore includes an unlimited set of compounds.*	944-22-9
5	*N*,*N*-Dialkyl (Me, Et, *n*-Pr or *i*-Pr) phosphoramidic dihalides *Precursors for Schedule 1.A.02 chemicals, tabun and analogues*  R^1 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) X = halide	
6	Dialkyl (Me, Et, *n*-Pr or i-Pr) *N*,*N*-dialkyl (Me, Et, *n*-Pr or *i*-Pr)-phosphoramidates *Possible precursors for, or impurities, in Schedule 1.A.02 chemicals*  R^1 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr)	
7	Arsenic trichloride *Precursor for Schedule 1.A.05 chemicals, Lewisites* 	7784-34-1

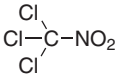
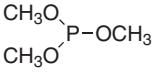
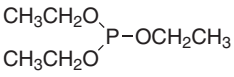
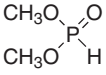
Appendix 1 (continued)

No.	Chemical/s	CAS number
8	2,2-Diphenyl-2-hydroxyacetic acid *Precursor for BZ* 	76-93-7
9	Quinuclidin-3-ol *Precursor for BZ* 	1619-34-7
10	*N*,*N*-Dialkyl (Me, Et, *n*-Pr or *i*-Pr) aminoethyl-2-chlorides and corresponding protonated salts *Precursors for Schedule 1.A.03 chemicals, V agents* $ClCH_2CH_2N(R^3)_2$ R^3 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr)	
11	*N*,*N*-Dialkyl (Me, Et, *n*-Pr or *i*-Pr) aminoethane-2-ols and corresponding protonated salts *Precursors for Schedule 1.A.03 chemicals, V agents* $HOCH_2CH_2N(R^3)_2$ R^3 = C1-C3 (Me, Et, *n-Pr*, *i*-Pr) Exemptions: *N*,*N*-Dimethylaminoethanol and corresponding protonated salts  *N*,*N*-Diethylaminoethanol and corresponding protonated salts  *These both have widespread industrial uses. Based on discussions after OPCW Proficiency Tests these chemicals are considered relevant and should be reported in a typical test as non-scheduled degradation products of V agents [6].*	108-01-0 100-37-8
12	*N*,*N*-Dialkyl (Me, Et, *n*-Pr or *i*-Pr) aminoethane-2-thiols *Precursors for Schedule 1.A.03 chemicals, V agents* $HSCH_2CH_2N(R^3)_2$ R^3 = C1-C3 (Me, Et, *n*-Pr, *i*-Pr) and corresponding protonated salts 	
13	Thiodiglycol: bis(2-hydroxyethyl)sulfide *Precursor for sulfur mustard* 	111-48-8
14	Pinacolyl alcohol: 3,3-Dimethylbutan-2-ol 	464-07-3

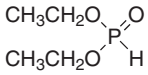
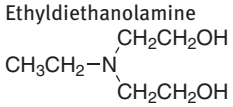
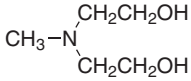
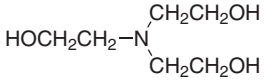
Appendix 1 (continued)

Schedule 3

The following criteria shall be taken into account in considering whether a toxic chemical or precursor, not listed in other Schedules, should be included in Schedule 3:
(a) It has been produced, stockpiled or used as a chemical weapon;
(b) It poses otherwise a risk to the object and purpose of this Convention because it possesses such lethal or incapacitating toxicity as well as other properties that might enable it to be used as a chemical weapon;
(c) It poses a risk to the object and purpose of this Convention by virtue of its importance in the production of one or more chemicals listed in Schedule 1 or Schedule 2, part B;
(d) It may be produced in large commercial quantities for purposes not prohibited under this Convention.

No.	Chemical	CAS number
A. Toxic chemicals		
1	Phosgene: Carbonyl dichloride 	75-44-5
2	Cyanogen chloride 	506-77-4
3	Hydrogen cyanide 	74-90-8
4	Chloropicrin: Trichloronitromethane 	76-06-2
B. Precursors		
5	Phosphorus oxychloride 	10025-87-3
6	Phosphorus trichloride 	7719-12-2
7	Phosphorus pentachloride 	10026-13-8
8	Trimethyl phosphite 	121-45-9
9	Triethyl phosphite 	122-52-1
10	Dimethyl phosphite 	868-85-9

Appendix 1 (continued)

No.	Chemical	CAS number
11	Diethyl phosphite 	762-04-9
12	Sulfur monochloride 	10025-67-9
13	Sulfur dichloride 	10545-99-0
14	Thionyl chloride 	7719-09-7
15	Ethyldiethanolamine 	139-87-7
16	Methyldiethanolamine 	105-59-9
17	Triethanolamine 	102-71-6

The schedules above list toxic chemicals and their precursors and are taken from the Convention [1, 4]. These schedules identify chemicals for the application of verification measures. The guidelines for inclusion in each schedule are also provided. Chemical structures, which are not provided in the text of the CWC, have been added by the authors for ease of reference, and additional comments in italics.

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[2] For details of the award of the 2013 Nobel Peace Prize to the OPCW, see the OPCW public website: https://www.opcw.org/special-sections/nobel-peace-prize-2013/, accessed on 1 June 2018.

[3] The statistics in this sentence were taken from the homepage of the OPCW public website at https://www.opcw.org/, accessed on 1 June 2018.

[4] The Annex on Chemicals to the CWC appears at www.opcw.org/chemical-weapons-convention/annexes/annex-on-chemicals/, accessed on 1 June 2018.

[5] An infographic of the schedules is available to download free-of-charge from www.opcw.org/fileadmin/OPCW/Science_Technology/Guide_to_Schedules.pdf, accessed on 1 June 2018.

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[15] For information on IUPAC, see https://iupac.org/, accessed on 1 June 2018.
[16] For information on CAS, see https://www.cas.org/, accessed on 1 June 2018.
[17] The current composition, terms of reference, rules of procedure, and documents of the OPCW SAB can be found at https://www.opcw.org/about-opcw/subsidiary-bodies/scientific-advisory-board/, accessed on 1 June 2018.
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[19] For an article by the then OPCW SAB Chairperson, Professor Alejandra Graciela Suárez (of Argentina), on the role and activities of the SAB, refer to *OPCW Today* **3**, 6 (2014). https://www.opcw.org/fileadmin/OPCW/OPCW_Today/OPCW_Today_-_Vol_3_No_1.pdf, accessed on 1 June 2018.
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