



OPCW

Scientific Advisory Board

Twenty - Third Session
18 – 22 April 2016

SAB-23/WP.1
28 April 2016
ENGLISH only

**RESPONSE TO THE DIRECTOR-GENERAL'S REQUEST TO THE
SCIENTIFIC ADVISORY BOARD TO PROVIDE FURTHER ADVICE
ON SCHEDULED CHEMICALS**



Annex

RESPONSE TO THE DIRECTOR-GENERAL'S REQUEST TO THE SCIENTIFIC ADVISORY BOARD TO PROVIDE FURTHER ADVICE ON SCHEDULED CHEMICALS

1. RECCOMENDATIONS

1.1 The Scientific Advisory Board (SAB) has considered isotopically labelled scheduled chemicals and stereoisomers of scheduled compounds relating to the Convention according to the Director-General's requests (see Appendixes 1 and 2).

1.2 **Recommendation 1.** The SAB recommends that the molecular parent structure of a chemical should determine whether it is covered by a schedule entry. This is because:

(a) it is inappropriate to rely solely upon Chemical Abstracts Service (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;

(b) 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

(c) this advice is consistent with previous SAB views on this topic.¹

1.3 **Recommendation 2.** Inclusion of appropriate analytical data in the OPCW Central Agent Database (OCAD) for isotopically labelled relatives of scheduled compounds where available is recommended.

2. OBJECTIVE

2.1 At the Twenty-Second Session of the SAB in June 2015 [1]², the Technical Secretariat introduced a request from the Director-General (Appendixes 1 and 2) to make technical recommendations on how chemicals relevant to Schedules 1, 2 and 3 should be considered in relation to the Convention if they contain isotopic labels or can exist in distinguishable stereoisomeric forms; taking into account the SAB's previous views on CAS registry numbers [2].

¹ RG-2/DG.1, dated 28 February 2008, in paragraph 3.5 of its Annex.

² Numbers in square brackets refer to the numbered references on pages 10 – 12.

- 2.2 The Annex on Chemicals to the Convention comprises three schedules listing toxic chemicals and their precursors.^{3,4} They consist of generic descriptions of classes of chemicals, or chemical names (see Note 1 on page 10) accompanied by their CAS registry numbers (see Note 2 on page 10).
- 2.3 To meet in spirit the obligations in Article VI (paragraphs 1 and 2) of the Convention, and to ensure complete and accurate declarations by States Parties to the Convention, chemicals that fall under Schedules 1, 2, and 3 must be clearly identifiable.
- 2.4 Some isotopically labelled compounds and stereoisomers of scheduled chemicals have presented ambiguity as to whether they should be declared. This report provides a scientific analysis of the relationships between such chemicals and those specified in the schedules. It recommends how chemicals relevant to Schedules 1, 2 and 3 should be considered in relation to the Convention.

3. FINDINGS

- 3.1 Isotopic labelling is a commonly employed technique in the study of chemicals. The study of the stereoisomers is essential for understanding the action of molecules in natural processes. In relation to the Convention, isotopic labelling is used to develop analytical methods and to investigate the mechanisms of action of scheduled chemicals in natural processes.
- 3.2 The use of stereoisomers allows a better comprehension of the mechanisms of toxicity of chemical agents. The synthesis of pure isotopically labelled molecules and stereoisomers requires a high degree of skill and more expense than classical approaches to unlabelled or stereoisomeric mixtures of chemicals.
- 3.3 Isotopically labelled chemicals and stereoisomers of chemical agents are used mainly on a small scale in research laboratories to help develop protective measures.

4. ISOTOPES

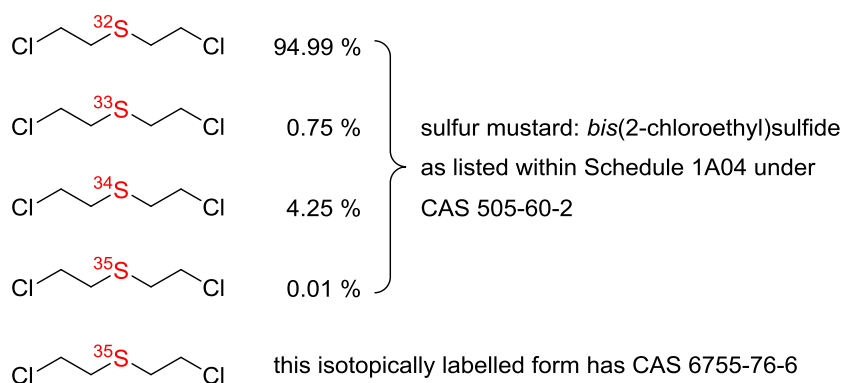
- 4.1 Isotopes are atoms of the same chemical element, having the same number of protons in the nucleus (same atomic number), but different numbers of neutrons in the nucleus (different atomic masses). Isotopes of the same element differ physically, for example slightly in mass, but are nearly identical chemically. Therefore they can be used as tracers in chemical and biological investigations.
- 4.2 The mechanism of action of chemical warfare agents is well understood in natural processes. Isotope substitution is regarded as the smallest structural change in a molecule. Thus, isotopically labelled chemical warfare agents are presumably as hazardous as their unlabelled counterparts listed in the schedules.

The Annex on Chemicals to the Convention appears at www.opcw.org/chemical-weapons-convention/annexes/annex-on-chemicals/

⁴ An infographic of the schedules is available at www.opcw.org/fileadmin/OPCW/Science_Technology/Guide_to_Schedules.pdf

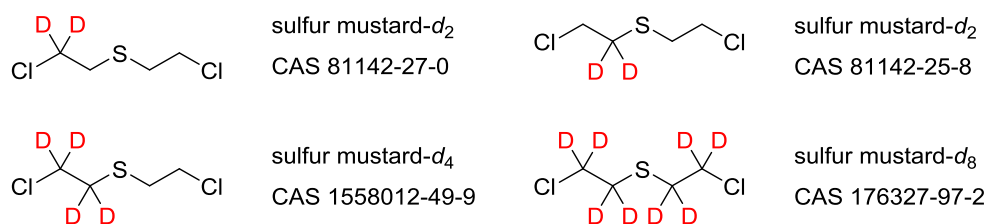
- 4.3 Chemicals in the schedules are those whose structures contain the most abundant naturally-occurring isotopes (^1H , ^{12}C , ^{15}N , ^{16}O , ^{31}P) and CAS numbers assigned to these chemicals assume that they only comprise these isotopes. This is an oversimplification. Scheduled chemicals do not exist solely as composites of these most-abundant isotopes. They exist as mixtures of chemicals containing different isotope ratios (the ratios of each isotope will depend on its natural abundance). A good example is sulfur mustard - bis(2-chloroethyl)sulfide - in Schedule 1A04 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) [3] (Figure 1). ^{33}S - and ^{34}S -sulfur mustard have not been assigned CAS numbers. ^{35}S -Sulfur mustard has been isolated [4] and assigned CAS number 6755-76-6, which differs from the CAS number of sulfur mustard in Schedule 1A04. This could mean that ^{35}S -sulfur mustard might not be identified for declaration, even though it is a minor constituent of the sulfur mustard identified in Schedule 1A04 by CAS number 505-60-2.

FIGURE 1: PERCENTAGES OF CAS 505-60-2 CONSTITUENTS CALCULATED FROM THE NATURAL ABUNDANCES OF ISOTOPES OF SULFUR



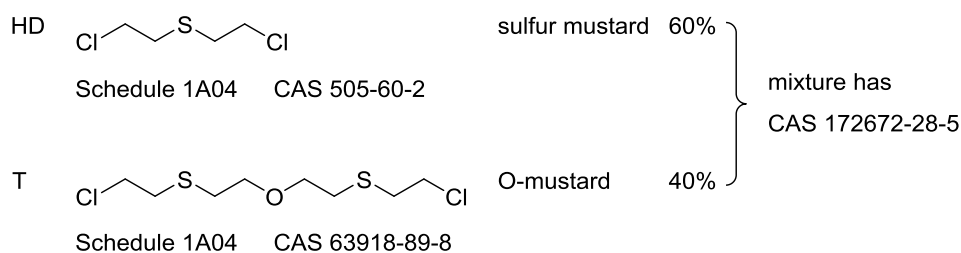
- 4.4 If the only chemicals considered to be covered by Schedule 1, for example, are those with CAS numbers listed in the Annex on Chemicals to the Convention, then the deuterium (*d*)-labelled sulfur mustards [4-10] in Figure 2 - all of which are likely to be as hazardous as the sulfur mustard in Schedule 1A04 under CAS 505-60-2 - might not be considered 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. Consideration to removing this ambiguity, based on the advice herein, should be given to strengthen further the intent and purpose of the Convention.

FIGURE 2: D DENOTES A DEUTERIUM ATOM IN PLACE OF A HYDROGEN ATOM [4-10]



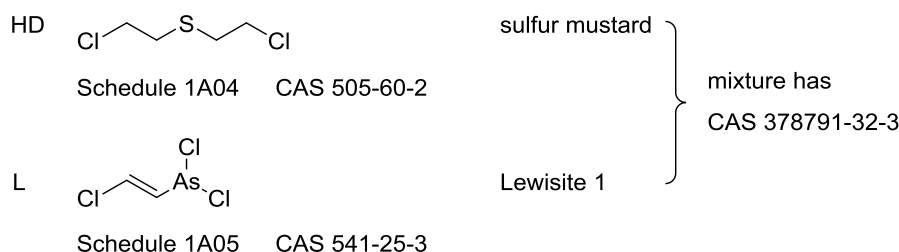
- 4.5 Furthermore, reliance on CAS numbers to identify scheduled chemicals does not address how to identify mixtures of toxic chemicals for accurate declaration. For example, a mixture of 60:40 percent by weight of sulfur mustard HD (Schedule 1A04, CAS 505-60-2) and oxygen mustard (O-mustard) T (Schedule 1A04, CAS 63918-89-8) has been used to fill chemical weapons in the past [11,12]. This so-called HT mixture has a CAS number (Figure 3) that is absent from the schedules.

FIGURE 3: HT



- 4.6 Another example is a mixture of sulfur mustard (Schedule 1A04, CAS 505-60-2) and Lewisite 1 (L) (Schedule 1A05, CAS 541-25-3) which has also been weaponised historically [13-16]. This mixture has a CAS number different from those of its pure components (Figure 4).

FIGURE 4: HD AND L MIXTURE

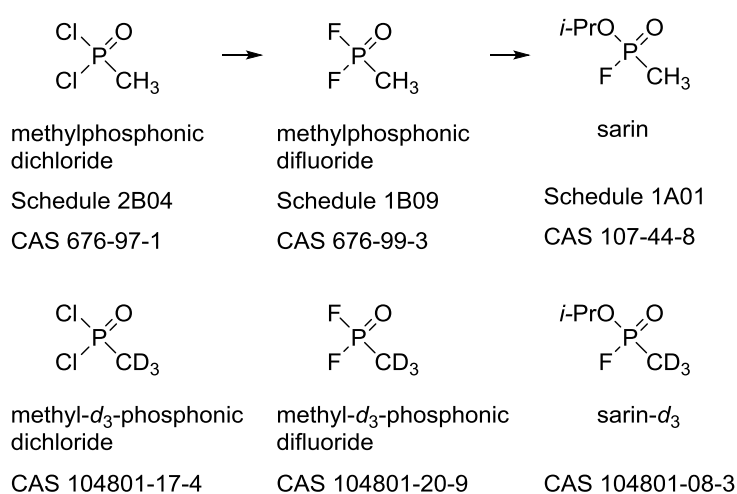


- 4.7 Another illustrative example is the route to sarin production from methylphosphonic dichloride [17,18] through methylphosphonic difluoride [19] to sarin (Figure 5). Isotopically labelled counterparts are shown underneath. All three have different CAS numbers to those present in the schedules for the unlabelled variants. Therefore they

might not be identified as scheduled chemicals, yet sarin- d_3 is likely to be as hazardous as sarin.

- 4.8 Schedule 1A01 that contains sarin under the generic name of *O*-alkyl alkylphosphonofluoridates defines only structures with P-methyl, ethyl, and *n*- or *i*-propyl groups; these can be interpreted to comprise CH₃, C₂H₅, and C₃H₇ and not deuterated variants, for example CD₃, C₂D₅, and C₃D₇. This interpretation could be applied to all such scheduled chemicals. Clearly all isotopically labelled versions of such compounds should be considered scheduled chemicals.

FIGURE 5: CONVERSION OF METHYLPHOSPHONIC DICHLORIDE TO SARIN



- 4.9 One way to capture these isotopically labelled chemicals within the schedules is to acknowledge that they are identical for the purposes of declaration to their unlabelled counterparts already specified in the schedules.

5. STEREOISOMERS

- 5.1 Stereoisomers are molecules that have the same molecular formula and sequence of bonded atoms (constitution) but differ in the orientation of their atoms in space [20]. They can be classified further, for example, into enantiomers or diastereoisomers:

- (a) **Enantiomer:** One of a pair of molecules that are mirror images of each other and non-superimposable by virtue of having a tetrahedral atom (e.g. carbon or phosphorus) with four different substituents bonded to it (this atom is a 'chiral centre' and the molecule can be described as chiral). Enantiomers have the same physical properties, except for the direction they rotate a plane of polarized light; their interaction with different optical isomers of other compounds is governed by their chirality. As a result, different enantiomers may display different biological effects.
- (b) **Diastereoisomers:** Stereoisomers other than enantiomers, not related as mirror images. Diastereoisomers show differences in physical properties and some

differences in chemical behaviour towards achiral and chiral reagents. Chemical properties and biological effects of diastereoisomers can be similar.

- 5.2 **Some toxic chemicals exist as enantiomers (e.g. organophosphorus nerve agents) or diastereoisomers (e.g. the nerve agent soman).** Nerve agent stereoisomers (enantiomers and/or diastereoisomers) show differences in biological activity as revealed by the data in the Table. The (+)-enantiomer, so-called because it rotates a plane of polarized light to the right, is usually a weaker inhibitor of the enzyme acetylcholinesterase (AChE) (inhibition disrupts the functioning of the Central Nervous System, CNS) and less toxic than the (-)-enantiomer, so-called because it rotates polarized light to the left. The racemic mixture, a 1:1 molar ratio of each enantiomer, is denoted by the prefix (\pm) and has a biological activity that is the sum contribution of the two enantiomers.

TABLE 1: THE EFFECT OF NERVE AGENT STEREOCHEMISTRY ON ANTICHOLINESTERASE ACTIVITY AND ACUTE LETHALITY OF NERVE AGENT STEREOISOMERS [17, 21-23]

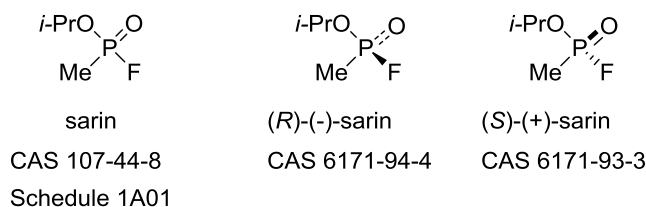
Stereoisomer	Rate constant for AChE inhibition at 25 °C ($M^{-1} \text{ min}^{-1}$) ^a	LD ₅₀ mouse ($\mu\text{g kg}^{-1}$)
(+)-tabun	4×10^5	837 ^b
(-)-tabun	2×10^6	119 ^b
(\pm)-tabun	-	208 ^b
(+)-sarin	$< 3 \times 10^3$ ^d	-
(-)-sarin	1×10^7	41 ^b
(\pm)-sarin	-	83 ^b
C(+)P(+)-soman	$< 5 \times 10^3$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

^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: the (-)-cyclosarin enantiomer, where the P-isopropoxy group in sarin is replaced by a cyclohexyloxy group, inhibits AChE more strongly than (\pm)-cyclosarin and is the more toxic isomer [22], in line with the trend revealed in the table.

- 5.3 Standard synthetic pathways to chemical agents 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.
- 5.4 Sarin (*O*-isopropyl methylphosphonofluoridate) listed in Schedule 1A01 and defined by CAS number 107-44-8 is understood to comprise an approximately equal mixture of its enantiomers [24-28]. This mixture is denoted (\pm)-sarin. However, the pure enantiomers have different CAS numbers: CAS number 6171-94-4 for the more toxic

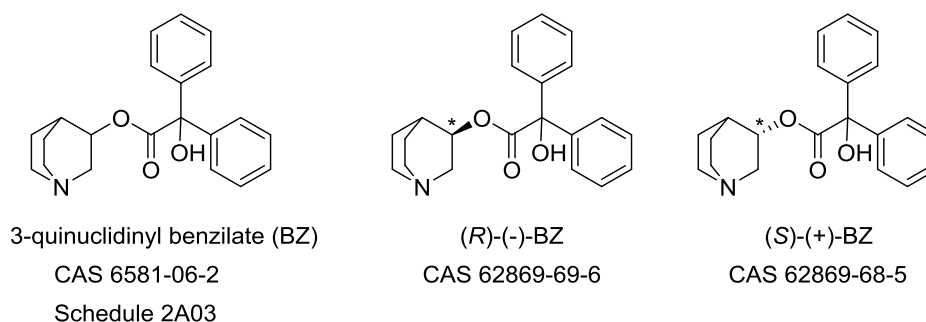
(*R*)-(-)-sarin and CAS number 6171-93-3 for the less toxic (*S*)-(+)-sarin (Figure 6). As both are highly toxic and have similar properties to the (\pm)-material specified in Schedule 1A01, they should be treated similarly.

FIGURE 6: SARIN AND ITS STEREOISOMERS



- 5.5 Another example is provided by the CNS-acting chemical BZ (3-quinuclidinyl benzilate) [29]. It features in Schedule 2A03 under CAS number 6581-06-2. This compound can exist as enantiomers: (*R*)-(-)-BZ and (*S*)-(+)-BZ (producing this material under non-enantioselective conditions would produce a mixture of the two enantiomers in a 1:1 ratio). Both enantiomers will cause behavioural effects in humans, with (*R*)-(-)-BZ at least 20 times more potent than the (*S*)-(+)-stereoisomer in causing behavioural effects after subcutaneous administration to dogs [30]. 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, so the Convention should treat both equally. Therefore all possible stereoisomers of BZ should be captured by Schedule 2A03.

FIGURE 7: BZ AND ITS STEREOISOMERS. THE CHIRAL CARBON ATOM IN THE QUINUCLIDINYL GROUP IS MARKED BY AN APOSTROPH.



- 5.6 These examples, like those in Appendixes 1 and 2, are illustrative and more could be provided. However the SAB does not find this necessary: the general points have been clearly illustrated already.

6. CONCLUSIONS

- 6.1 The SAB recommends that isotopically labelled or stereoisomeric variants of scheduled chemicals should be interpreted as belonging to the schedule that includes the parent structure. And that the structure of a chemical, regardless of its isotope pattern or spatial orientation of atoms, should determine whether that chemical falls within the Convention schedules. A principal reason for this is that:
- (a) Isotopically labelled scheduled chemicals and stereoisomers of scheduled chemicals, and mixtures thereof, have nearly identical chemical properties. Because of the huge number of isotopically labelled and stereoisomeric scheduled chemicals theoretically obtainable, it is inappropriate to rely solely on CAS numbers specified in the schedules for identifying scheduled chemicals.
- 6.2 The fact that the parent chemicals are on the schedules obligates the States Parties to treat isotopically labelled and stereoisomeric forms of such chemicals appropriately for declaration and verification purposes.
- 6.3 Inclusion of appropriate analytical data in OCAD for isotopically labelled relatives of scheduled compounds where available is recommended.

NOTES

1. A chemical name is a common name or one standardised according to nomenclature rules of the International Union of Pure and Applied Chemistry (IUPAC).
2. The Chemical Registry System was developed by CAS from work started in the early 1960s after the perfection of an algorithm for generating a unique and unambiguous computer language representation of the molecular configuration of each chemical (www.cas.org). 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 various names used for the chemical in the literature and its Chemical Abstracts index name.

REFERENCES

1. Report of the Twenty-Second Session of the Scientific Advisory Board held on 8-12 June 2015, SAB-22/1, 21 July 2015, Annex 2, pp. 27-29.
2. RG-2/DG.1, dated 28 February 2008, in paragraph 3.5 of its Annex.
3. M Berglund, M E Wiesser. Isotopic compositions of the elements 2009 (IUPAC Technical Report). *Pure Appl. Chem.* **83** (2011) 397-410.
4. J M Harrison. Synthesis of isotopically labelled 1,1'-thiobis(2-chloroethane) and some related compounds. *J. Labelled Comp. & Radiopharm.* **29** (1991) 1175-1180.
5. J W Lown, R R Kogarty, A V Joshua. Synthesis of specifically deuterium labeled sulfur and oxygen ether side-chain-extended antileukemic (2-chloroethyl)nitrosoureas and study of their products and pathways of decomposition under physiological conditions. *J. Org. Chem.* **47** (1982) 2027-2033.
6. L Yue, Y Wei, J Chen, H Shi, Q Liu, Y Zhang, J He, L Guo, T Zhang, J Xie *et al.* Abundance of four sulfur-mustard-DNA adducts *ex vivo* and *in vivo* revealed by simultaneous quantification in stable isotope dilution-ultrahigh performance liquid chromatography-tandem mass spectrometry. *Chem. Res. Toxicol.* **27** (2014) 490-500.
7. J C Bournsnel, G E Francis, A Wormal. Studies on mustard gas (β,β' -dichlorodiethyl sulfide) and some related compounds. III. Preparation and use of mustard gas containing (a) radioactive sulfur and (b) deuterium. *Biochem. J.* **40** (1946) 743-745.
8. T E Banks, J C Bournsnel, G E Francis, F L Hopwood, A Wormal. Studies on mustard gas (β,β' -dichlorodiethyl sulfide) and some related compounds. IV. Action on proteins (studied with the aid of radioactive sulfur). *Biochem. J.* **40** (1946) 745-756.
9. Z Nie, Q Liu, J Xie. Improvements in monitoring the N-terminal valine adduct in human globin after exposure to sulfur mustard and synthesis of relevant chemicals. *Talanta* **85** (2011) 1154-1159.

10. A Fidder, D Noort, A L de Jong, H C Trap, L P A de Jong, H P Benschop. Monitoring of *in vitro* and *in vivo* exposure to sulfur mustard by GC/MS determination of the *N*-terminal valine adduct in haemoglobin after a modified Edman degradation. *Chem. Res. Toxicol.* **9** (1996) 788-792.
11. C M Timperley, R M Black, M Bird, I Holden, J L Mundy, R W Read. Hydrolysis and oxidation products of the chemical warfare agents 1,2-bis[(2-chloroethyl)thio]ethane Q and 2,2'-bis(2-chloroethylthio)diethyl ether T. *Phosphorus, Sulfur, and Silicon* **178** (2003) 2027-2046.
12. S P Harvey, L L Szafraniec, W T Beaudry. Hydrolysis and biodegradation of the chemical warfare vesicant agent HT. *US patent 6017750 A 20000125* (2000).
13. B Muir, B J Slater, D B Cooper, C M Timperley. Analysis of chemical warfare agents I. Use of aliphatic thiols in the trace level determination of Lewisite compounds in complex matrices. *J. Chromatogr. A* **1028** (2004) 313-320.
14. B Muir, S Quick, B J Slater, D B Cooper, M C Moran, C M Timperley, W A Carrick, C K Burnell. Analysis of chemical warfare agents II. Use of thiols and statistical experimental design for the trace level determination of vesicant compounds in air samples. *J. Chromatogr. A* **1068** (2005) 315-326.
15. W Carrick, L Fernee, D Francis. Heat characteristics of chemical warfare agents. *J. Thermal Analysis Calorimetry* **79** (2005) 101-106.
16. V G Sakharovskii, V I Tugushov, E V Kasparova, A M Zyakun, A I Kochergin, A M Boronin. Mineralization of detoxification products of yperite-lewisite mixture. *Russian J. Appl. Chem.* **74** (2001) 259-264.
17. C M Timperley. *Best Synthetic Methods – Organophosphorus (V) Chemistry*, Elsevier, Oxford, UK, 2015.
18. J L Mundy, J M Harrison, P Watts, C M Timperley. Isotopically labelled phosphorus compounds: some deuterated methyl and ethyl derivatives. *Phosphorus, Sulfur, and Silicon* **181** (2006) 1847-1857.
19. D G Ott, M J Reisfeld, T W Whaley. Syntheses of isotopically labelled threat agents. *Synth. Appl. Isot. Labelled Compd. Proc. Int. Symp. 2nd* (1986) 409-414.
20. A W A D McNaught (Ed.). *Compendium of Chemical Terminology, Second Edition*, International Union of Pure and Applied Chemistry (IUPAC), Blackwell Scientific Publications, Oxford, UK, 1997.
21. A J Ooms, H L Boter. Stereospecificity of hydrolytic enzymes in their reaction with optically active organophosphorus compounds I. The reaction of cholinesterases and paraoxonase with *S*-alkyl *p*-nitrophenyl methylphosphonothiolates. *Biochem. Pharmacol.* **14** (1965) 1839-1846.

22. S P Harvey, J E Kolakowski, T C Cheng, V K Rastogi, L P Reiff, J J DeFrank, F M Raushel, C Hill. Stereospecificity in the enzymatic hydrolysis of cyclosarin (GF). *Enzyme Microb. Technol.* **37** (2005) 547-555.
23. D B Cooper, J M Harrison, T D Inch. Preparation, stereochemistry and some reactions of 1,3,2-oxazaphospholanes. *Tetrahedron Lett* **31** (1974) 2697-2700.
24. H E T Spruit, H C Trap, J P Langenberg, H P Benschop. Bioanalysis of the enantiomers of (\pm)-sarin using automated thermal cold-trap injection combined with two-dimensional gas chromatography. *J. Anal. Toxicol.* **25** (2001) 57-61.
25. Z Miao, H Li, Y Zhou, R Feng, G Li. ^{19}F -NMR study on separation and identification of stereoisomers of nerve agents. *Junshi Yixue Kexnuynan Yuankan* **23** (1999) 205-208.
26. J R Smith, J J Schlager. Gas chromatographic separation of the stereoisomers of organophosphorus chemical warfare agents using cyclodextrin capillary columns. *J. High Res. Chromatogr.* **19** (1996) 151-154.
27. G R Van den Berg, D H J M Platenberg, H P Benschop. Organophosphorus compounds. XI. Stereochemistry of Grignard displacement reactions at phosphorus in isopropyl methylphosphonohalogenates. *Rec. Trav. Chim. Pays-Bas* **91** (1972) 929-934.
28. H L Boter, A J J Ooms, G R van der Berg, C van Dijk. Synthesis of optically active isopropyl methylphosphonofluoridate (sarin). *Rec. Trav. Chim. Pays-Bas* **85** (1966) 147-150.
29. M Rehavi, S Maayani, M Sokolovsky. Enzymic resolution and cholinergic properties of (\pm)-3-quinuclidinol derivatives. *Life Sci.* **21** (1977) 1293-1302.
30. A Meyerhöffer. Absolute configuration of 3-quinuclidinyl benzilate and the behavioral effect in the dog of the optical isomers. *J. Med. Chem.* **15** (1972) 994-995

Appendix 1

DIRECTOR-GENERAL'S REQUEST TO THE SCIENTIFIC ADVISORY BOARD TO PROVIDE ADVICE ON ISOTOPICALLY LABELED SCHEDULED CHEMICALS

1. The Chemical Weapons Convention allows States Parties to possess chemicals that are intended for purposes not prohibited by the Convention:

Each State Party has the right, subject to the provisions of this Convention, to develop, produce, otherwise acquire, retain, transfer and use toxic chemicals and their precursors for purposes not prohibited under this Convention. (Article VI, paragraph 1).

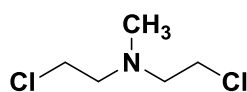
2. With this right come obligations, including:

Each State Party shall adopt the necessary measures to ensure that toxic chemicals and their precursors are only developed, produced, otherwise acquired, retained, transferred, or used within its territory or in any other place under its jurisdiction or control for purposes not prohibited under this Convention. To this end, and in order to verify that activities are in accordance with obligations under this Convention, each State Party shall subject toxic chemicals and their precursors listed in Schedules 1, 2 and 3 of the Annex on Chemicals, facilities related to such chemicals, and other facilities as specified in the Verification Annex, that are located on its territory or in any other place under its jurisdiction or control, to verification measures as provided in the Verification Annex. (Article VI, paragraph 2).

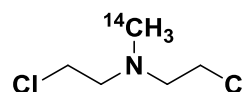
3. To meet these obligations, and to ensure complete and accurate declarations by the Convention States Parties to the OPCW⁵, chemicals that fall under Schedules 1, 2, and 3 of the Convention must be clearly identifiable.
4. Some isotopically labelled Schedule 1 and Schedule 2 chemicals have presented ambiguity as to how they should be declared.
5. Isotopic labelling is a commonly employed technique in the study of chemicals; including in the development of analytical methods for chemical agents and in the study of mechanisms of action of chemical agents used to develop protective measures.
6. The Annex on Chemicals to the Convention identifies chemicals using generic descriptions of classes of chemicals and for each scheduled chemical a specific name and corresponding Chemical Abstracts Service (CAS) registry number.

⁵ Parts VI, VII and VIII to the Convention's Annex on Implementation and Verification set out the relevant requirements.

7. CAS numbers are intended to provide a unique, unmistakable identifier for chemical substances. However, a chemical will have different CAS registry numbers assigned to its various analogues containing isotopic labels⁶.
8. The Scientific Advisory Board (SAB) has cautioned that “there is not necessarily a one-to-one relationship between CAS registry numbers and chemical structures”, and has advised that CAS registry numbers be considered aids to identification (RC-3/DG.1, dated 29 October 2012, paragraph 76; see also RC-2/DG.1, dated 28 February 2008, in paragraph 3.5 of the Annex).
9. The following two examples are illustrative of the ambiguity that can arise with isotopically labelled chemicals:
- (a) bis(2-chloroethyl)methylamine (HN2) is listed in Schedule 1.A.06 with CAS registry number 51-75-2. The ¹⁴C isotopically labelled molecule, bis(2-chloroethyl)methyl-¹⁴C]-amine, has not been assigned a CAS registry number; if only the exact name and/or CAS number as listed in Schedule 1.A.06 were considered, the ¹⁴C labelled nitrogen mustard agent might not be identified as a scheduled chemical; see the structures below:



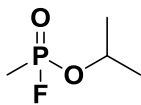
Bis(2-chloroethyl)methylamine

Bis(2-chloroethyl)methyl-[¹⁴C]-amine

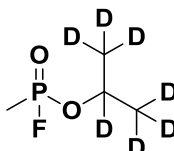
- (b) another example involves three isotopic variations of sarin (in the illustration overleaf): **(i)** isopropyl methylphosphonofluoridate **(ii)** isopropyl-d₇ methylphosphonofluoridate and **(iii)** isopropyl methyl-d₃-phosphonofluoridate. The first of these is sarin as listed in Schedule 1.A.01 (with CAS number 107-44-8). The other two are deuterated analogs of sarin. It has been argued that **(ii)** should be considered under Schedule 2.B.04 rather than under Schedule 1.A.01, and that **(iii)** should not be considered under any Chemical Weapons Convention schedule because the “methyl” (of methyl, ethyl, propyl and isopropyl) corresponds to “CH₃” only, and not the deuterated analog.

⁶

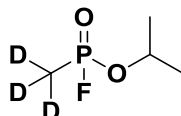
A CAS number is a unique numerical identifier assigned by CAS to every chemical substance described in the open scientific literature from at least 1957 to the present, including those of synthetic and biological origin. As a CAS number is only assigned if the chemical in question has been reported in the open scientific literature, some isotopically labelled chemicals related to those scheduled will not have a CAS number assigned to them.



(i) Isopropyl methylphosphonofluoridate



(ii) Isopropyl-d7 methylphosphonofluoridate



(iii) Isopropyl methyl-d3-phosphonofluoridate

10. The Director-General requests the Scientific Advisory Board (SAB) to:
- make technical recommendations on isotopic labelling of chemicals relevant to Schedule 1, 2 and 3 under the Chemical Weapons Convention – in light of the SAB's previous advice on CAS registry numbers (RC-2/DG.1, dated 28 February 2008, in paragraph 3.5 of the Annex); and
 - 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 Chemical Weapons Convention.

Appendix 2

DIRECTOR-GENERAL'S REQUEST TO THE SCIENTIFIC ADVISORY BOARD TO PROVIDE ADVICE ON STEREOISOMERS OF SCHEDULED CHEMICALS

1. The Convention allows States Parties to possess chemicals that are intended for purposes not prohibited by the Convention:

Each State Party has the right, subject to the provisions of this Convention, to develop, produce, otherwise acquire, retain, transfer and use toxic chemicals and their precursors for purposes not prohibited under this Convention. (Article VI, paragraph 1).

2. With this right come obligations, including:

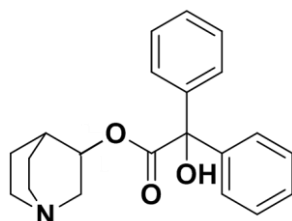
Each State Party shall adopt the necessary measures to ensure that toxic chemicals and their precursors are only developed, produced, otherwise acquired, retained, transferred, or used within its territory or in any other place under its jurisdiction or control for purposes not prohibited under this Convention. To this end, and in order to verify that activities are in accordance with obligations under this Convention, each State Party shall subject toxic chemicals and their precursors listed in Schedules 1, 2 and 3 of the Annex on Chemicals, facilities related to such chemicals, and other facilities as specified in the Verification Annex, that are located on its territory or in any other place under its jurisdiction or control, to verification measures as provided in the Verification Annex. (Article VI, paragraph 2).

3. To meet these obligations, and to ensure complete and accurate declarations by CWC States Parties to the OPCW⁷, chemicals that fall under Schedules 1, 2, and 3 of the Convention must be clearly identifiable.
4. Some Schedule 2 chemicals that can exist as distinct stereoisomers have presented ambiguity in how they should be declared.
5. Stereoisomers are molecules with identical molecular formula, which differ in their three-dimensional spatial orientation of atoms. Stereoisomers are defined by orientation of atoms around chiral within the molecular structure (a chiral center is an atom, usually a carbon atom, with four unique substituents bonded to it in a tetrahedral arrangement). Stereoisomers of some chemicals can be isolated (e.g. BZ).
6. The Annex on Chemicals to the Convention identifies chemicals covered by the Verification Annex using generic descriptions of classes of chemicals and for each

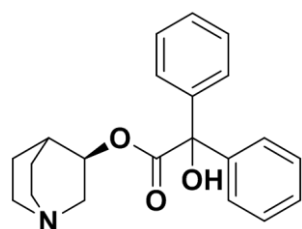
⁷ Parts VI, VII and VIII to the Convention's Annex on Implementation and Verification set out the relevant requirements.

scheduled chemical a specific chemical name and its corresponding Chemical Abstracts Service (CAS) registry number.

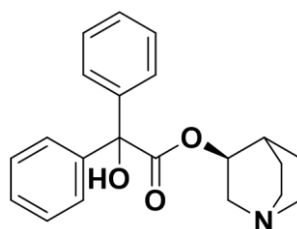
7. CAS numbers are intended to provide a unique, unmistakable identifier for chemical substances. However, a given stereoisomer of a chemical will have a unique CAS registry number that differs from the CAS registry number assigned, for example, for the related compound having undefined stereochemistry (e.g. a mixture of stereoisomers)⁸.
8. The Scientific Advisory Board (SAB) has cautioned that “there is not necessarily a one-to-one relationship between CAS registry numbers and chemical structures” and has advised that CAS registry numbers be considered aids to identification (RC-3/DG.1, dated 29 October 2012, paragraph 76; see also RC-2/DG.1, dated 28 February 2008, in paragraph 3.5 of the Annex).
9. 3-Quinuclidinyl benzilate (BZ; **(i)** in the illustration below) illustrates the ambiguity for stereoisomers. BZ is listed in Schedule 2.A.03 to the Convention, with its chemical name and CAS number 6581-06-2; its structure is not shown in the Convention. BZ can exist, however, in two different stereoisomeric forms (**(ii)** and **(iii)**): these stereoisomers have been assigned CAS numbers 62869-69-6 (**(ii)**) and 62869-68-5 (**(iii)**). If only the exact name and/or CAS number as listed in Schedule 2.A.03 were considered, stereoisomers might not be identified as scheduled chemicals.



(i) (3-quinuclidinyl benzilate with stereochemistry not indicated, CAS number 6581-06-2)



(ii) (CAS Number 62869-69-6)
(*R*)-3-quinuclidinyl benzilate



(iii) (CAS Number 62869-68-5)
(*S*)-3-quinuclidinyl benzilate

8

A CAS number is a unique numerical identifier assigned by CAS to every chemical substance described in the open scientific literature from at least 1957 to the present, including those of synthetic and biological origin. As a CAS number is only assigned if a chemical (in this case, a specific stereoisomer) has been reported in the open scientific literature, some stereoisomers of scheduled chemicals may not have a CAS number assigned to them.

10. The Director-General requests the Scientific Advisory Board (SAB) to make technical recommendations on how stereoisomers of chemicals relevant to Schedule 1, 2 and 3 under the Chemical Weapons Convention should be considered in relation to the Convention, taking into account the SAB's previous advice on CAS registry numbers (RC-2/DG.1, dated 28 February 2008, in paragraph 3.5 of the Annex).

--- 0 ---