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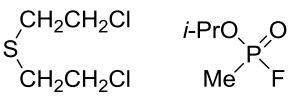
Graphical abstract

Review of, and advice given on, chemical weapons sample storage and stability, to assist chemical weapons-related forensic studies worldwide



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Abstract

The Scientific Advisory Board (SAB) of the Organisation for the Prohibition of Chemical Weapons (OPCW) has provided advice on the long-term storage and stability of samples collected in the context of chemical weapons investigations. The information they compiled and reviewed is beneficial to all laboratories that carry out analysis of samples related to chemical warfare agents and is described herein. The preparation of this report was undertaken on request from the OPCW Director-General. The main degradation products for chemicals on the Schedules in the Annex on Chemicals of the Chemical Weapons Convention are tabulated. The expertise of the 25 scientists comprising the SAB, a review of the scientific literature on environmental and biomedical sample analysis, and answers to a questionnaire from chemists of nine OPCW Designated Laboratories, were drawn upon to provide the advice. Ten recommendations to ensure the long-term storage and stability of samples collected in relation to the potential use of chemical weapons were provided and are repeated here for the consideration of all laboratories worldwide.

Keywords

Chemical Warfare Agent; Chemical Forensics; Organisation for the Prohibition of Chemical Weapons (OPCW); OPCW Scientific Advisory Board; Scheduled Chemical; Stability.

1. Introduction

The Chemical Weapons Convention (hereinafter "the Convention") is an international disarmament treaty that prohibits the development, production, stockpiling, acquisition and use of chemical weapons and requires the nations (the "States Parties") subject to the treaty to destroy any chemical weapons and related production facilities they may possess [1]. The Convention entered into force in 1997 and as of January 2018 has 192 States Parties, leaving only four States outside its obligations (these are the Democratic People's Republic of Korea, Egypt, Israel, and South Sudan). Implementation of the Convention includes a verification regime that allows on-site inspections and data monitoring of relevant chemical-related activities within the States Parties. This regime functions to verify that these activities are consistent with the objectives of the Convention. The Organisation for the Prohibition of Chemical Weapons (OPCW), an international organisation based in The Hague, The Netherlands, functions as the implementing body of the Convention. The OPCW was awarded the Nobel Peace Prize in 2013 for its 'extensive efforts to eliminate chemical weapons' [2] and continues to work to free the world permanently of chemical weapons.

Inspections are critical to the implementation of the Convention. OPCW inspectors are responsible for conducting three types of inspections: (a) routine inspections of chemical weapons-related facilities and chemical industry facilities that use certain 'dual-use' chemicals (i.e. chemicals that can be used for both peaceful and prohibited purposes); (b) short-notice challenge inspections, which can be conducted at any location on the territory of any State Party about which another State Party has concerns regarding possible non-compliance; and (c) investigations of alleged use (IAUs) of chemical weapons. Inspectors, who are selected from experts in their respective technical fields (chemistry, chemical engineering, munitions, health and safety, and a number of other relevant areas), are recruited from across the States Parties of the Convention and specially trained to conduct inspections in accordance with the intent and purpose of the Convention.

The only way to unambiguously confirm the presence of chemicals relevant to the Convention during inspections is to use analytical chemistry [3]. Analysis can be quantitative, for example

to ensure that chemical agent concentrations fall below a permitted threshold when subjected to neutralization processes during destruction, or qualitative to confirm if a relevant chemical is present. Inspections of industrial facilities can also be conducted with sampling and analysis using a mobile laboratory. Mission instruments used in these on-site inspections are maintained and certified under an International Organisation for Standardization (ISO) 17025 accredited quality system, by the OPCW Laboratory.

The Convention (within its Verification Annex) also contains provisions to analyse samples off-site. This is particularly important for politically-sensitive missions, such as challenge inspections or IAUs. For off-site analysis the OPCW depends on an international network of OPCW-designated partner laboratories [4]. To maintain designation, the laboratories must have an accredited quality system and participate successfully in Proficiency Tests organised by the OPCW Laboratory (accredited under ISO 17043) at least once a year [3,4].

This system has created a robust network of laboratories that act as a deterrent to non-compliance by adding high levels of confidence to the verification regime. The scientific rigour of proficiency testing, following criteria in the ISO 17025 quality system, and OPCW quality management system [5-8], ensures this high level of confidence. The laboratories must receive grades of AAA or AAB in their last three tests (an A grade is awarded to laboratories that identified all spiking chemicals in a test and have no reporting errors, while a B grade indicates a missed spiking chemical or a reporting error). Laboratories receiving more than one B grade or lower grades are suspended and cannot receive authentic samples for analysis. The test scheme has zero tolerance for false positives. A laboratory reporting a false positive in a Proficiency Test fails the test and loses its designation status.

The Convention contains within it an Annex on Chemicals consisting of three schedules of chemicals that are of high relevance to chemical disarmament and security, due to their historical and known uses as chemical warfare agents and precursors to such agents. Proficiency testing focuses on chemicals from these schedules. Reviewing the schedules (see the Appendix to this paper) reveals that the number of possible reportable chemicals is extensive (e.g. Schedule 2.B.04, which includes chemicals containing a phosphorus atom to which is bonded one methyl, ethyl or propyl group, but no further carbon atoms, includes an indeterminate number of possible phosphorus (III) and (V) compounds). Furthermore, some of the spiking chemicals in Proficiency Tests may not be present in any available spectral databases. These facts, together with the strict performance requirements already outlined,

ensure that proficient laboratories must maintain the highest level of analysis capabilities to keep their designation. In the early years of the Proficiency Tests, gas chromatography-mass spectrometry (GC-MS; electron impact and chemical ionisation) was the analytical technique of choice. Today, additional methodologies are used in a complementary way, and these include: GC with a flame photometric detector (used to detect sulfur and phosphorus) or thermionic specific detector (used to detect nitrogen and phosphorus) or atomic emission detector (multi-element detector), GC-MS/MS, GC-high resolution MS, liquid chromatography (LC)-MS, LC-MS/MS, LC-high resolution MS, nuclear magnetic resonance (NMR) spectroscopy (most often ^{1}H and ^{13}C, and ^{19}F and ^{31}P when applicable), and Fourier transform infrared (IR) spectroscopy [9-12].

OPCW Designated Laboratories require a chemical synthesis capability to make authentic standards for analytical data-matching, particularly when spectra are unavailable in databases. In addition to commercial databases of analytical information, the OPCW maintains a database of chemicals scheduled under the Convention. This is the OPCW Central Analytical Database (OCAD) [10] and is available to all States Parties of the Convention. The OCAD features over 6000 mass spectra, 5200 retention indices, 1400 NMR spectra and 1000 IR spectra. In October 2017, the OPCW Executive Council approved the first set of non-scheduled chemicals for inclusion in the OCAD [13].

Analysis of environmental samples can be used to identify the presence of chemical agents (and/or their degradation products and/or impurities carried over from production). To provide evidence of whether a suspected human casualty has been exposed to a chemical agent requires the analysis of biomedical samples, preferably blood and/or urine as they are easily collected [14,15]. Procedures for proving people have been exposed to chemical warfare agents (CWAs) through biomedical sample analysis have advanced significantly over the last decade. Besides the analysis of free agents and their metabolites, adducts of CWAs with biomolecules such as DNA and proteins are of prime importance, as they permit retrospective identification of exposure over longer time periods due to their persistence in the body. Forensic verification of a fatal poisoning in the Syrian Arab Republic in 2013 by the organophosphorus nerve agent sarin has been recently reported by two OPCW Designated Laboratories and illustrates this persistency [16]. Low concentrations of relevant chemicals in biomedical samples can require trace analysis in the sub-parts-per-billion range and the search for new relevant biomarkers is a continuing enterprise.

The OPCW conducts Proficiency Tests on environmental and biomedical samples, and designates laboratories for analysis of one or both types of sample. The designated laboratory network as of 31 August 2017 is shown in Figure 1; there are 24 laboratories located across 17 States Parties. The OPCW Laboratory, in close cooperation with its partner laboratories, has developed the proficiency testing scheme over the past 24 years, including making updates to its implementation over time. It is essential to constantly review whether the testing scheme is still meeting its requirements, follows developments in analytical chemistry, and is relevant with respect to real-world samples that the OPCW has been receiving since the United Nations (UN) led mission that investigated the 2013 Ghouta sarin attack in the Syrian Arab Republic [15,16].

In the way described, the OPCW, together with its partner laboratories, has been able to create a mechanism for the analysis of relevant authentic samples that is robust, and operates at an extremely high scientific standard, to implement effectively the "trust but verify" principle embodied in the Convention and its Verification Annex. The proficiency test participants have analysed samples in different matrices, identified spiking chemicals that cannot be found in analytical databases, and avoided 'pitfalls' set by the Sample Preparation Laboratories within the designated laboratory network. These measures have allowed the OPCW to have high confidence in the chemical analysis conducted by the designated laboratories [17]. Recommended Operating Procedures (ROPs) for analysis in the verification of chemical disarmament have been produced through international collaboration with expert laboratories working in the field of Convention-related analytical chemistry; these ROPs are available in the VERIFIN "Blue-Book" which was most recently updated in December 2017 [18]. When the designated laboratories are called upon to perform an off-site analysis, the samples will be split between two laboratories (in two States Parties) where the laboratories will carry out the analysis blindly to one another. In order for a result of the detection of a specific chemical to be accepted, both laboratories must confirm the presence of the specific chemical identified within the sample.

The advice outlined in this report was provided to the OPCW Director-General in 2016 (Figures 2 and 3). Since that time an OPCW Fact-Finding Mission (FFM) [19], has reported on new incidents, in particular in Ltamenah, Hama Governorate (March 2017) [20] and Khan Shaykhun, in the Syrian Arab Republic (April 2017) [21,22], where the use of sarin (or a sarin-like nerve agent that degrades to form methylphosphonic acid) was confirmed. Attribution of the use of chemical agents is outside the mandate of the FFM and the previous UN led Mission in 2013 that included OPCW inspectors in the inspection team. The information collected through the FFM was provided to an OPCW-UN Joint Investigative Mechanism (JIM) for further review [23]. In its final Seventh Report, the JIM stated that it was confident that a non-State actor (Daesh) was responsible for the use of sulfur mustard in Umm Hawsh in the Syrian Arab Republic on 15 and 16 September 2016, and that Syrian Arab Army forces were responsible for the release of sarin at Khan Shaykhun on 4 April 2017 [24]. The latter conclusion however, has been contested by some States Parties at both the United Nations Security Council (UNSC) and the OPCW; the mandate for the JIM was also discontinued by the UNSC in November 2017. It should also be noted that the JIM report does not represent findings from a court of law. Just prior to the Khan Shaykhun incident, a murder in Malaysia was reported to have involved the organophosphorus nerve agent VX [25], underscoring further the importance of chemical analysis in relation to the investigation of CWAs, and the timeliness of the advice on sample storage and stability described herein. Note that the SAB provides independent scientific advice to the OPCW Director-General and is not involved in specific incidents or investigations.

2. Advice from the SAB

Before presenting the SAB's advice on sample storage and stability, the role and constitution of the SAB itself warrants a brief explanation. The SAB is a subsidiary body of the OPCW, enabling the Director-General to render specialised advice in science and technology to OPCW policy-making bodies and States Parties. The SAB reports to the Director-General, who then makes the Board's reports available, alongside his own response, to the States Parties and the public. The SAB consists of 25 members, each of whom is an expert in one or more technical fields relevant to the Convention. SAB members serve in their individual capacity as independent experts. The SAB members are nominated by their respective States Parties, and the Director-General appoints members from the candidates put forth, keeping in mind the

candidates expertise and the need for geographical balance. Members are appointed for a three year term and are eligible to serve for two consecutive terms. Members are drawn from universities, industry, defence organisations and other institutions. Only citizens of the Convention's States Parties are eligible for SAB membership. Every year the SAB elects a Chair and Vice-Chair from its members. Further information on the SAB and its activities is available from the OPCW [26-28].

Returning to the topic of this paper, to be fully prepared to analyse any chemical potentially present in a wide range of types of samples in support of operational missions, the OPCW must be able to store samples over several years and analyse them with high accuracy at any point in time. The diversity of sample types containing Convention-relevant chemicals - such as nerve and blister agents, and immediate precursors and degradation products - is potentially vast [29], and could include:

(a) Relatively pure samples;

(b) Liquid (including extracts) and solid samples containing either relatively high levels or trace levels of the chemicals of interest;

(c) Highly heterogeneous unprocessed samples – such as soil, metal fragments, paint chips, fragments of highly absorbent material, or wipes – containing relatively high levels or trace levels of the chemicals of interest; and

(d) Biomedical samples, such as blood, plasma, urine, and tissue.

In November 2015, the OPCW Director-General requested the SAB to address three overarching questions (Supplementary Material, Appendix A):

(a) Given the current storage conditions in the OPCW Laboratory, how quickly and through what process could the aforementioned types of samples degrade to a point where analysis of the samples would likely no longer return credible results?

(b) What are the best-practice conditions for long-term storage of the aforementioned types of samples?

(c) Given these best-practice storage conditions, how quickly and through what process could the aforementioned types of samples degrade to a point where analysis of the samples would likely no longer return credible results?

Before answering these questions, it was necessary for the SAB to comment on the OPCW off-site verification mechanism in light of 'credible results' referred to in questions (a) and (c) above. The SAB noted that the analytical findings of the Designated Laboratories from analysis of samples collected in OPCW investigations will always be scientifically accurate because of the stringent checks and balances in place within the operating procedures [30]: the findings will always return 'credible results' ('credible' is defined in the Oxford English Dictionary as 'able to be believed; convincing'). The results of the analyses will always be convincing and withstand scrutiny both scientifically and legally, especially if presented as evidence in court. The integrity of the procedures established in OPCW Designated Laboratories provides necessary safeguards and thus protects the off-site analysis process from any suggestion of tampering. It was with these important points in mind that the Director-General's questions could be answered in turn:

(a) Given the current storage conditions in the OPCW Laboratory, how quickly and through what process could the aforementioned types of samples degrade to a point where analysis of the samples would likely no longer return credible results?

Any chemical stored for a sufficiently long time, no matter what the storage conditions, can degrade to one or more products. If the chemical degrades entirely and is no longer observable in the sample, scientists can often reconstruct the identity of the original chemical from analysis of its degradation products. These products in a sense constitute a 'memory' of the original chemical. The situation for CWAs and related chemicals, such as precursors, is no different: their concentration may reduce upon storage, although their degradation products will increase in concentration. This change, allowing the identity of the degraded chemical to be pieced together from the molecules constituting the degradation products, makes chemical analysis a powerful tool for retrieving evidence of chemical weapons use. Samples may also contain by-products of the synthetic route used to produce the CWA, as well as unreacted starting materials, which will further enhance their analytical value. To visualise how molecular degradation products can be used to reconstruct the identity of the original CWA, the non-scientist may wish to think about reconstructing a broken object, such as a vase, from its fragments. Similarly, in chemical forensics, the identity of a CWA or precursor can be reconstructed from the types of degradation products and impurities observed through sample analysis. It must be noted however, if the agent or precursor is initially present only at trace levels, prolonged storage may result in adsorption of the original chemical and/or its degradation product(s) to the container walls, for example. In such cases re-analysis could

result in the original chemical and/or its degradation product(s) not being detected, due to their presence in extremely low concentration(s), at levels below the detection limits of the analytical method employed.

Also, for chemical samples generally, the degradation products themselves can sometimes be unstable and degrade to simpler compounds that are more distant in structure than the initial component of the sample. The nature of a sample can also change if a compound or its degradation products are volatile and escape from a poorly sealed container. It is also possible that samples or their degradation products could be reactive and rather than degrade, could form new compounds by combining with other components or impurities in the sample. Finally, samples or their degradation products can polymerize to give products that are insoluble in solvents, and therefore not easily analysed by the usual techniques. Note that disassembly of organic compounds occurs in ways that are sometimes less obvious that one might predict.

The storage conditions used by the OPCW Laboratory will inevitably and naturally lead to loss of intact original chemicals by degradation in many cases (this phenomenon is a natural process and occurs in every laboratory in the world). It is impossible to put a precise time on how long any chemical will take to degrade, as shelf-life or degradation rate depends on the chemical structure, matrix, presence of further chemicals (e.g. stabilisers) and storage conditions, as well as the initial concentration of the chemical. It is only possible to estimate, with considerable uncertainty, a likely storage time, and impossible to state accurately when the various sample types will degrade to a point where analysis would not identify the intact original chemical(s).

However, it is possible to state that the intact original chemical(s) in the sample types stored in the OPCW Laboratory might degrade naturally in, at worst, weeks to months, and at best, months to years. In some cases, degradation is so slow that the intact agent is present for many decades. The analysis of samples in which the chemicals of interest have degraded will return credible analytical results, but with less specific information. The characteristic degradation compounds will still contain the molecular evidence for proving CWA use, or in the case of other investigations, the presence of a Convention-related chemical.

The main degradation of CWAs, and other Convention-related chemicals, in environmental samples occurs through reaction with water (hydrolysis) or oxygen in air (oxidation). To reduce the potential for degradation in the samples, as little time as possible should elapse from

the time of collection of any sample to the time of analysis; lengthy delays of weeks to years may diminish the concentration of the intact original chemicals in the samples, but does not diminish their usefulness as evidence in IAUs or other Convention-related investigations.

Recommendation 1.

Samples should be analysed as soon after collection as possible and the need for storage eliminated or, less favourably, the storage time minimised. Prompt analysis should be viewed as urgent, as the intact original chemicals will provide the strongest basis for confirming the use of chemicals prohibited by the Convention. (This is because the sample stability, and potential impacts of any matrix or environmental factors on the stability of any Convention-relevant chemicals in the sample, will not be known prior to analysis.)

Recommendation 2.

Further work on the storage of samples just after sampling and during transport to the OPCW Laboratory, sample handling during splitting, handling and storage of samples at the OPCW Laboratory, should be pursued.

(b) What are the best-practice conditions for long-term storage of the different types of samples?

The SAB reviewed the scientific literature, and the answers to a SAB questionnaire returned by nine OPCW Designated Laboratories, on the best-practice conditions for the sample types described. Based on the findings, to optimise the conditions for reduced degradation of the Convention-relevant chemicals in the samples, the SAB makes the following recommendations:

Recommendation 3.

Commercial chemical samples should be stored in certified clean glass containers with Teflon-lined caps in the dark: those in

(i) Schedules 1.A.01, 1.A.02, 1.A.03, 1.A.06, 1.B.09, 1.B.10, 1.B.11 and 1.B.12 at -18 °C under argon (to enable stability for 5-10 years).

(ii) Schedules 1.A.04 and 1.A.05 at room temperature (for stability > 10 years).

(iii) Schedule 1.A.08 (ricin) as a precipitate in 6 M ammonium sulfate at 4 °C (for stability > 10 years).

Recommendation 4.

Extracts of chemicals should be made in dichloromethane and stored in certified clean glass containers at 4 °C with Teflon-lined caps in the dark, to ensure stability of the intact original chemical for up to one year (swabs or wipes should be analysed within one month of collection or otherwise disposed of due to likely storage instability; wherever possible they should be extracted as soon as possible into dichloromethane and the extracts stored instead).

Recommendation 5.

Highly heterogeneous unprocessed samples – such as soil, metal fragments, paint chips, or fragments of highly absorbent material – containing relatively high levels or trace levels of the chemicals of interest, should be stored in sealed glass or high-density polyethylene containers at -18 °C under an inert gas (e.g. argon or nitrogen), to guarantee the stability of the samples for up to 6 months. For samples containing any moisture (e.g. soil), -80 °C could be better than -18 °C.

Recommendation 6.

Biomedical samples – for example, urine or plasma – should be stored in polypropylene or polyethylene terephthalate containers in a freezer at -80 °C (except for whole blood, which should be refrigerated at 4 °C) to ensure the integrity of the samples for as long as possible (up to several years).

Recommendation 7.

Larger volumes of chemicals/samples should be split into subsamples and the subsamples used for repeated analytical manipulations. This will reduce the number of warming-cooling cycles the samples have to encounter. This is important, especially for materials stored in a freezer or deep freeze (-80 °C). It will also help to minimise degradation of the chemical(s) in the unused portions of samples.

Recommendation 8.

Samples of neat Scheduled chemicals required for long-term banking within the OPCW Laboratory should be flame-sealed in glass ampoules under an inert gas (e.g. argon or

nitrogen); the use of the flame-sealed ampoule technique appears to offer some storage and shipping advantages for which there is evidence [31].

(c) Given these best-practice storage conditions, how quickly and through what type of process could the different types of samples degrade to a point where analysis of the samples would likely no longer return credible results?

The previous comments in this section on the uncertainties of prediction of shelf-lives of chemicals should be noted. Based on the review herein of processes by which Convention-relevant chemicals degrade, the SAB assesses that it is difficult, given the incomplete knowledge worldwide of the fate of CWAs and other CWC-relevant chemicals in different matrices, to specify precisely when the analysis of a sample would likely no longer identify the intact original chemicals. Degradation could be catalysed by minor impurities and rates of decomposition could vary significantly. The best-practice storage conditions provided in answer to the previous question will extend the time the original chemical in the sample will persist. Although some loss of this chemical may occur even under these conditions, the analysis of the samples will return credible analytical results, but with less specific information. The characteristic degradation products and other chemical residues (such as synthesis by-products and unreacted starting materials) will still provide the molecular evidence necessary to recognise CWA production, confirm the use of chemical weapons, or inform other Convention-related compliance testing.

Further information on the provenance of the chemicals in a sample might be accessible through chemical forensics methodologies. In this respect, the SAB recognises that attribution of CWA use will become easier as the science of chemical forensics advances. These observations led the SAB to propose two additional recommendations relevant to addressing the OPCW Director-General's questions:

Recommendation 9.

The OPCW should monitor advances in sampling and analysis, and with the SAB, any new innovations relevant to chemical forensics. (The SAB started to consider this topic in 2016 and held an international workshop on the subject in Helsinki that summer; see Section 4 for further information.)

Recommendation 10.

A reference sample collection at the OPCW Laboratory should be kept to provide a range of chemical forensic options for current and future samples suspected of containing Convention-relevant chemicals [32-38].

2. Findings

2.1. Processes by which relevant chemicals degrade

The scientific literature describes processes by which CWAs and other Convention-relevant chemicals degrade. While the information is incomplete, compilations of data do exist [39-48]. These suggest that many CWAs and other Convention-relevant chemicals, if pure, and stored in the absence of water, can last for years without appreciable deterioration. This high stability has enabled them to be stockpiled historically. In some cases, 'stabilisers' (chemical additives) have been added to preserve them from degradation. Processes that affect chemical storage are physical (evaporation and absorption) and/or chemical (mainly hydrolysis, oxidation, and polymerisation). Degradation is a complex phenomenon that is still not fully understood.

CWAs generally react with water and often other nucleophilic chemicals. Nerve agents (tabun, sarin, soman, and VX) and vesicants (sulfur mustard, nitrogen mustards, and Lewisites) hydrolyse at a rate dependent on their aqueous solubility and susceptibility to attack by water molecules [49-51]. Sulfur and nitrogen mustards have low solubility in water and this protects them to an extent from hydrolytic degradation. This is demonstrated by the current hazards posed by sea-dumped chemical munitions containing sulfur mustard, despite the fact that disposal occurred decades ago [52,53]. This is largely due to the formation of a protective coating caused by reaction of the sulfur mustard with its hydrolysis products, to give an insoluble polymer comprised of long-chain sulfonium compounds.

It is the hydrolysis of nerve and blister agents during storage, in the environment or human body, which usually results in their degradation (by one or multiple pathways depending on their chemical structure) and detoxification [45,46]. The rate of hydrolysis depends on temperature and pH for environmental samples and for biomedical samples (37 °C, pH 7.4) on the presence of additional substances that may catalyse hydrolysis (e.g. enzymes such as carboxylesterase present in plasma [54]). Some chemicals of interest can further undergo oxidation by oxygen in the air, or during metabolism [41-48], as shown in Figure 4 for the

nerve agent *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (VX) and bis(2-chloroethyl)sulfide (sulfur mustard or HD).

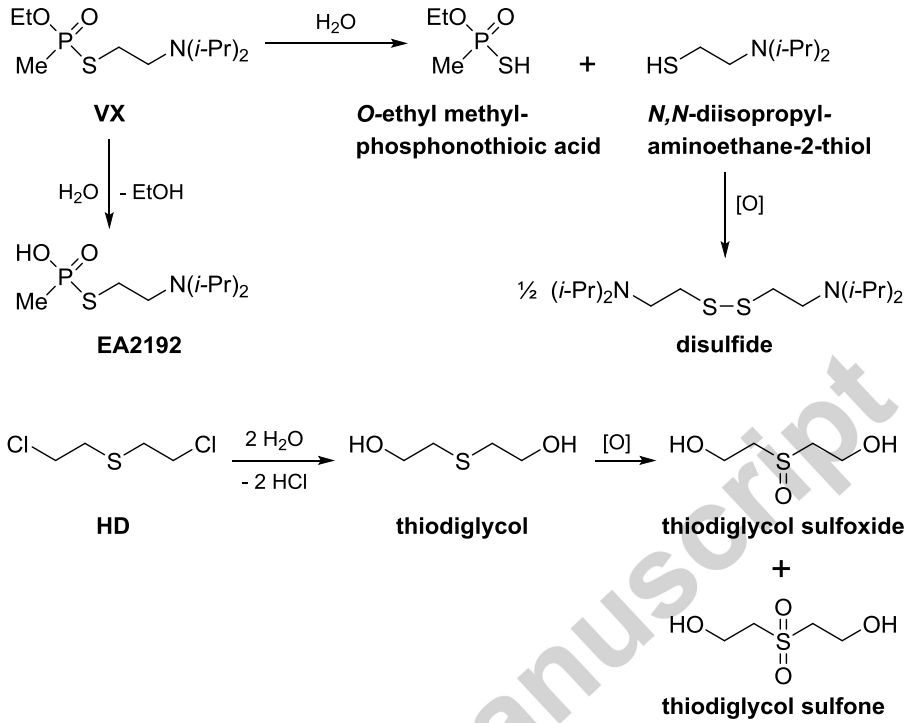
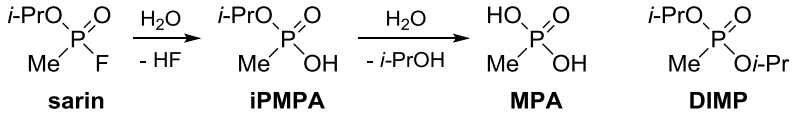


Figure 4. Degradation of VX (*top*) or HD (*bottom*) occurs through hydrolysis then oxidation.

Hydrolysis of VX is complex and pH dependent and can produce EA2192, which, like VX, is a potent anticholinesterase of high toxicity. The thiol produced by one of the VX hydrolysis pathways is oxidised by oxygen in the air to a disulfide. Thiodiglycol from HD hydrolysis oxidises to thiodiglycol sulfoxide and thiodiglycol sulfone.

Oxidation has also been employed for the destruction [55-58] and decontamination [59,60] of Convention-relevant chemicals. Oxidation is only possible when the affected atom is not in its maximum oxidation state. The resilient P-C bond remains intact throughout environmental hydrolysis of nerve agents such as *O*-isopropyl methylphosphonofluoridate (sarin) [42,51], while the P-F bond, then more slowly the *i*-PrO-P bond, is cleaved by water. The P-CH_3 motif in the hydrolysis products isopropyl methylphosphonic acid (iPMPA) and methylphosphonic acid (MPA) indicates the prior presence of sarin [61,62], especially when found together with the production impurity diisopropyl methylphosphonate (DIMP) (Figure 5). Atoms in low

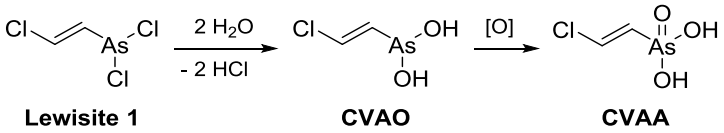
oxidation states, such as sulfur in thiols RSH or sulfides RSR can oxidise to give disulfides RSSR, sulfoxides RS(O)R or sulfones RSO_2R, respectively. In addition to the formation of disulfides, thiols can also form sulfenic, sulfinic, and sulfonic acids (in order of increasing oxidation state), particularly when disulfide formation is disfavoured in dilute solution.



sarin **iPMPA** **MPA** **DIMP**

Figure 5. Sarin reacts with environmental moisture to provide iPMPA. This reacts slowly with water with the loss of isopropanol to provide MPA. The discovery of sarin, iPMPA, MPA and DIMP by the United Nations investigating team, from analysis of soil samples collected after the 21 August 2013 attack in Ghouta in the Syrian Arab Republic, confirmed that sarin-filled rockets had been deployed [63,64].

Sulfur and nitrogen mustards degrade along several pathways: (a) to give vinyl species, e.g. $HOCH_2CH_2SCH=CH_2$ from elimination of hydrogen chloride from the initial product of hydrolysis of HD; (b) through cyclisation, for example of HD, during hydrolysis, e.g. to give 1,4-thioxane; (c) sulfonium or quaternary nitrogen salt formation from intermolecular reaction of hydrolysis products of sulfur and nitrogen mustards, respectively, and (d) the oxidation of HD to form the sulfoxide and sulfone. This complexity of degradation is typical for mustard-type vesicants bearing at least one 2-chloroethyl group ($ClCH_2CH_2$-). The arsenical agent Lewisite 1 contains a trivalent arsenic(III) atom and hydrolyzes rapidly with loss of hydrogen chloride to 2-chlorovinylarsenous oxide (Lewisite oxide, CVAO). This then oxidises to 2-chlorovinylarsonic acid (CVAA) where the arsenic atom has the +5 oxidation state (Figure 6) [45,50]. This is another example of a hydrolysis and oxidation process of CWA degradation. Note that this process can occur in environmental samples containing vesicant agents on storage, or decontamination, and will be time dependent. Fortunately, the hydrolysis and oxidation products contain much of the structural information of the CWA itself and are indirect proof of the prior presence of the CWA [42].



Lewisite 1 **CVAO** **CVAA**

Figure 6. Lewisite 1 hydrolysis to CVAO, which retains the vesicant and toxic properties of Lewisite 1 [65]. CVAO oxidises to CVAA which is not appreciably vesicant, but some toxicity remains because of the presence of the arsenic atom.

CWAs and other Convention-relevant chemicals also react with certain solvents and care should be taken to choose an appropriate solvent for short-term storage. HD and some nerve agents react readily with low molecular-weight alcohols. Nucleophilic solvents, such as these, should be regarded as unsuitable. In one Designated Laboratory, organophosphorus nerve agents are regarded as stable in isopropanol, and HD is stored in hexane. Care is required in the choice of other solvents for CWAs and other Convention-relevant chemicals. Care must also be taken to select appropriate grades of solvent for extraction and storage of CWAs and other Convention-relevant chemicals. Drying solvents wherever possible is likely to minimise unwanted degradation via hydrolysis. Some commercial solvents contain more water than others: acetonitrile is an example of one which could have a relatively high water content; all commercial solvents, including those sold for chromatographic applications, could contain significant quantities of water (up to 500 parts per million). Some sample solutions containing reactive chemicals, such as sulfur mustard sulfone, prepared in dimethyl sulfoxide (DMSO) should be stored in a vacuum desiccator rather than a refrigerator due to the strong hygroscopic nature of this solvent. Gas chromatographic performance during sample analysis can also be a storage consideration; the preferred solvents for chromatography include hexane, dichloromethane, and ethyl acetate.

Technical difficulties associated with assessing CWA purity are considerable and to some extent have confounded definitive data on the subject. No single analytical technique is suited to measuring all components of mixtures simultaneously. For example, the acidic hydrolysis products of nerve agents cannot directly be analysed by GC and data based solely on this technique could give an artificially high impression of purity. Likewise, low thermal stability of some impurities can lead to a false impression of agent purity. The most suitable technique for assessing CWA purity is NMR spectroscopy. Even using this technique, more than one measurement is required to account for the possibility of the presence of non-phosphorus containing degradation products or stabilising chemicals; and detailed work is required to

characterise the range of possible degradation products in mixtures [39-48]. Sensitivity limitations can also prevent the characterisation of lower concentration impurities by NMR spectroscopy. However, it remains the technique of choice for routine purity assessments of CWAs and Convention-related chemicals, noting that trace impurities in samples - such as unreacted starting materials, synthetic by-products, and stabilisers - can provide valuable information on the history and perhaps provenance of the chemicals.

Stability studies on neat chemical agents are normally based on the storage of material for use as reference or surety material to support research for protective purposes, as permitted by the Convention. In general, high purity (>95%) chemical agents are required for such work. In some cases, the storage of neat chemical agents so that they remain at this purity specification requires careful control of storage and use conditions. The storage of small quantities of CWA is likely to result in large headspaces above the agent. These smaller quantities of CWAs may be less stable than larger quantities of CWA stored in vessels with a reduced headspace. Frequency of use is also important: one Designated Laboratory has shown that solutions (~1 $mg \cdot mL^{-1}$) of CWAs degrade faster when opened weekly compared to those that remain unopened for a longer time period [66,67].

The stability of low concentration solutions of CWAs for quantitative purposes has been studied in one Designated Laboratory by gas chromatography with flame photometric detection (GC-FPD) and by GC-MS [66,67]. It was difficult to control instrument response over sufficient time (months) to be certain that the differences in quantitation resulted from degradation rather than changes in instrument response. This resulted in low concentration solutions of CWAs for quantitative work being stored for no more than one month (because of absence of reliable evidence to support longer-term storage). Note, however, the difference in requirements for a CWA needed for quantitative analysis and that required for a Convention-related investigation where confirmation of "presence" is a key criterion.

The US Environmental Protection Agency compared the stability of dilute solutions of CWAs in dichloromethane and hexane in screw-capped vials and flame-sealed ampoules [68]. The analytical measurements contained some uncertainty, but in general flame-sealed ampoules resulted in greater stability than screw-capped vials. In most cases, degradation, where observed, was confirmed by complementary techniques (observation of products by GC-MS). Of the CWAs in this study, sarin and VX were most susceptible to degradation during storage; up to a maximum of 80% degradation of VX occurred over 1 year. Solutions of CWAs in

dichloromethane were more stable than those in hexane. The study highlighted that CWA impurities can affect storage stability; VX degraded faster in the presence of sarin.

Insufficient information is available to ascertain if CWA degradation in solution is concentration dependent. It is often assumed that low concentration solutions will be less stable because of a higher water-to-analyte ratio or because of the possible adsorption to the container walls, but this requires further study.

The rate of degradation of CWAs in the environment depends on many factors: the precise nature of the chemical agent and contaminated surface, and the temperature. For example, snow contaminated with sarin, soman, tabun, VX, and HD was analysed after exposure for 1, 4, 7, 15, and 30 days under Norwegian winter conditions [69]. After 15 days, the nerve agents tested were present in concentrations sufficient to allow positive verification and quantitative analysis by GC-MS. After 30 days, the concentration of sarin, tabun and HD had fallen below the limits of detection; the analysis could only identify soman and VX. HD freezes on contact with snow and does not penetrate it as easily as the other agents. This illustrates the difficulty of predicting CWA fate as physical and chemical factors affect the persistence of each agent differently, making their stability in environmental matrices difficult to forecast accurately.

The examples provided illustrate the general principle that most CWAs are unstable in the presence of moisture and hydrolyse at different rates to give characteristic products. These products can transform further - in the environment or body - via oxidation to provide non-toxic, often stable products [70]. Detection of the starting agent, hydrolysis and/or oxidation products, has been reported from analysis of samples collected days to weeks after a chemical attack [42,70].

Identification of CWAs in biomedical samples – e.g. blood, plasma, urine, or tissue – is also possible, but CWAs do not remain intact in the body for long. The products of hydrolysis/oxidation are much more likely to be detected. Sometimes a CWA enters the body and reacts with a specific amino acid of a protein present in the bloodstream (e.g. albumin, haemoglobin, acetylcholinesterase, or butyrylcholinesterase) to give an addition product (adduct). DNA-adducts are also reported, mainly with HD. The adduct retains some of the structural information of the CWA and provides information on the CWA used. Unambiguous identification of adducts and/or urinary metabolites, using mass spectrometry, can provide evidence of CWA exposure. Such an approach has been applied successfully to the retrospective identification of poisoning by HD [71-106], nitrogen mustards [107-110],

Lewisite [111-116], organophosphorus nerve agents [71,117-173], the incapacitant BZ [174], phosgene [175] and hydrogen cyanide [176].

Approaches to the analysis of biomedical samples to assess exposure to nerve agents [177] and chemical forensics relevant to the Convention [178] have been reviewed by the OPCW Laboratory. An edition of the peer-reviewed journal "Analytical and Bioanalytical Chemistry" on *Analysis of Chemicals Relevant to the Chemical Weapons Convention*, guest-edited by scientists from the OPCW Laboratory [3], also contains pertinent information.

How long after human exposure to CWAs can biomarkers be detected is not easily predicted, especially given the paucity of confirmed human exposures, and difficulty of extrapolating data from animal experiments. The problem extends to estimating how long samples containing such biomarkers can be stored without loss of information critical as evidence to an IAU or other CWC-related investigation. In environmental samples, hydrolysis/oxidation products are likely to remain retrievable by solvent extraction sometime after the CWA was disseminated. In this case, there may be an opportunity to visit the samples at a later date, maintaining the possibility of finding evidence of CWA use.

Biodegradation of CWAs by microorganisms might affect the storage of CWA samples. Biodegradation of organophosphorus compounds has been studied as a possible means of nerve agent destruction [179]. Only a few microorganisms screened to date and isolated have the capacity to degrade CWAs, and this capacity is limited at present. Data on the microbial degradation of CWAs in samples, and CWA-containing sample matrices, are largely lacking.

Characteristic degradation products for chemicals in Schedules 1, 2 and 3 in the Annex on Chemicals to the Convention [1] are summarised in the Appendix [180-222]. These products are not exhaustive, but cover many of those of anticipated relevance to IAUs or other Convention-related investigations. Mass spectra of many of the products are already in the OCAD.

Based on this review of processes by which Convention-relevant chemicals degrade, it is assessed that it is difficult, given the incomplete knowledge worldwide of the fate of CWAs in different matrices, to specify precisely when analysis of a sample 'would likely no longer identify the intact original chemicals'. Analytical results, produced under stringent quality control in OPCW Designated Laboratories, are always 'credible'. The main conundrum is how long after sample collection and storage will key markers of CWA use, or other Convention-

prohibited activity, remain detectable? The passage of time will certainly lower the probability of identifying the original intact chemical(s), but the degradation products will remain detectable, and will be important in proving CWA use.

Only estimates can be provided to answer the question of the time window to ensure the integrity of the intact original chemicals in stored samples. To provide these estimates a questionnaire was composed (Supplementary Material, Appendix B) for the OPCW Designated Laboratories. Nine laboratories responded and their views on sample storage are collated and analysed in the next sub-section.

2.2. Responses from the OPCW Designated Laboratories

Best-practice sample storage conditions provided by OPCW Designated Laboratories in response to the SAB's questionnaire are discussed hereafter in order of sample type in the Director General's question, namely:

(a) Relatively pure samples (commercial, own-made, and solutions of chemicals).

(b) Samples containing chemicals of interest; including heterogeneous samples.

(c) Biomedical samples: including blood, plasma, urine, and tissue.

2.2.1. Relatively pure samples

Relatively pure samples have been subdivided into commercial chemicals, own-made chemicals, and solutions of chemicals, because of their different storage requirements, and are now discussed in turn:

Commercial chemicals: These should be stored in their original packaging in the dark at a temperature recommended by the manufacturer (room temperature, 4 °C, or -18 °C). Maximum storage times are chemical-dependent; the supplier expiration date should be used as an indication of shelf-life. Commercial chemicals can be used for the manufacturer's recommended storage time or stored until no longer required; purity checks before use are advised.

One Designated Laboratory noted that the ISO 17025 quality system required commercial chemicals to be purity checked at least every 2 years. (ISO 17025 is the main ISO standard used by testing and calibration laboratories. In many countries, it is the accreditation standard most laboratories must hold to be deemed technically competent. OPCW Designated Laboratories require this to be permitted to analyse environmental samples.) Another replied that to prolong storage life pure chemicals can be diluted with an inert solvent, such as acetonitrile or dichloromethane. A third Designated Laboratory estimated maximum storage times of 1, 3 and 5 year(s) for pure chemicals kept at -20 °C, 2-10 °C, and 25 °C respectively (Table 1). Importantly, these comments refer to analytical standards and not analytical samples.

Table 1. Designated Laboratory responses: commercial chemicals.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Commercial, pure	General	room temperature												■	
		refrigerator											■		
		freezer (-18 °C)									■				
		original container		■									■	■	
		manufacturer recommendation		■											

Room temperature : usually 25 °C.

Own-made chemicals: These should be stored in glass, high-density polyethylene (HDPE) or Teflon containers, and resealed between uses. Those not accessed regularly, especially chemicals in Schedule 1, can be stored in sealed glass ampoules under an inert gas atmosphere (e.g. argon). The recommended storage temperature varies according to the chemical but -18 °C is preferred by most Designated Laboratories (Table 2) that responded to the questionnaire. The glass or plastic containers should be housed in containers made of metal (e.g. stainless steel) and these should contain active charcoal to absorb any accidental spillage of the chemicals. A Designated Laboratory commented that rare or difficult-to-obtain chemicals

should be stored indefinitely, noting that even impure samples could assist analysis at some point in future.

One Designated Laboratory with long-term experience provided guidelines for the best-practice storage of Schedule 1 chemicals, grouping them into classes according to storage requirements (Tables 2 and 3). In general, the purer the CWAs, the longer they stayed pure (although >95% purity at the start of the storage period was advised).

Table 2. Designated Laboratory responses: own-made chemicals.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Synthesized, pure	General	refrigerator											■		
		freezer (-18 °C)	■		■										■
		glass container	■		■								■		■
		HDPE container											■		
		Teflon lined caps													■
		argon atmosphere											■		
		sealed ampoules											■		
	Schedule 1 (general)	freezer (-18 °C)													■
		glass container													■
	Nerve agents	freezer (-18 °C)								■					■
		glass container								■					■
		Teflon lined caps													■
		argon atmosphere													■
	Vesicants	freezer (-18 °C)								■					■
		room temperature								■					■
		glass container													■
		glass stopper													■
	Sulfur mustard	Teflon lined caps													■
		sealed with wax													■
		argon atmosphere													■
		room temperature													■
		glass container													■
	Lewisite	Teflon lined caps													■
		argon atmosphere													■

Room temperature: usually 25 °C. HDPE: High-density polyethylene.

Table 3. Designated Laboratory responses: Schedule 1 chemicals and precursors.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Synthesized, pure	Nitrogen mustard hydrochloride salts	freezer (-18 °C) glass container Teflon lined caps argon atmosphere													
	Ricin	precipitate in 6 M NH_4SO_4 glass container Teflon lined caps													
	Schedule 1 precursors	freezer (-18 °C) glass container Teflon lined caps argon atmosphere													
	Methylphosphonic difluoride (DF)	freezer (-18 °C) Teflon container argon atmosphere													
	P-Cl precursors	freezer (-18 °C) glass container Teflon lined caps argon atmosphere													

Room temperature: usually 25 °C.

Additional information on best-practice storage conditions for Schedule 1 chemicals from this same Designated Laboratory are provided here, with additional data in square brackets from another Designated Laboratory:

- Schedule 1.A.01: *O*-Alkyl alkylphosphonofluoridates (e.g. sarin, soman)
- Schedule 1.A.02: *O*-Alkyl *N*,*N*-dialkylphosphoramidocyanidates (e.g. tabun)
- Schedule 1.A.03: *O*-Alkyl *S*-2-dialkylaminoethyl alkylphosphonothiolates (e.g. VX)
- Schedule 1.A.06: Nitrogen mustards (i.e. HN-1, HN-2, HN-3)

- Schedule 1.B.10: *O*-Alkyl *O*-2-dialkylaminoethyl alkylphosphonites (e.g. QL)
- Schedule 1.B.11: *O*-Isopropyl methylphosphonochloridate (i.e. chlorosarin)
- Schedule 1.B.12: *O*-Pinacolyl methylphosphonochloridate (i.e. chlorosoman)

Stored at -18 °C in glass containers with Teflon-lined caps in the dark under argon, degradation is slow: 5-10% over 5-10 years (except Schedule 1.B.10 chemicals which show 20-40% degradation over 5 years, as they are generally highly reactive).

[Pure samples (>95%) of sarin or soman store at room temperature - and cyclosarin, tabun, and V-agents store at -18 °C - for over a year. The storage stability of pure samples of V-agents is structure dependent and declines, in the absence of any added stabilisers, in the order: *O*-isobutyl *S*-2-diethylaminoethyl methylphosphonothiolate > *O*-ethyl *S*-2-diethylaminoethyl methylphosphonothiolate (VM) > *n*-butyl *S*-2-diethylaminoethyl methylphosphonothiolate > *O*-ethyl *S*-2-diisopropylaminoethyl methylphosphonothiolate (VX).]

[Tris(2-chloroethyl)amine (HN-3) stores for a month at -18 °C before visible degradation (discoloration and precipitation), but analysis shows the supernatant to be pure despite this time-related change.]

- Schedule 1.A.04: Sulfur mustards
- Schedule 1.A.05: Lewisite 1, Lewisite 2, Lewisite 3

Stored at room temperature in the dark under argon in glass containers with Teflon-lined caps, they are stable for over 10 years.

[Sulfur mustard stores at room temperature for decades. Lewisites 1, 2 and 3 store unchanged for over a year at room temperature.]

- Schedule 1.A.08: Ricin

Stored as a precipitate in 6 M ammonium sulfate at 4 °C in the dark in glass containers with Teflon-lined caps (insoluble if freeze-dried), the ricin is stable for over 10 years.

- Schedule 1.B.09: Alkylphosphonic difluorides

These moisture-sensitive liquids are stored at -18 °C in the dark under argon in Teflon containers. Under these conditions they degrade slowly (5-10% over 5-10 years).

[Perfluoroalkoxyalkane plastic is suitable for storing methylphosphonic difluoride (DF) or an equimolar mixture of methylphosphonic dichloride and DF (the so-called "di-di mixture"). Both DF and the "di-di mixture" will degrade slowly over a year when stored at room temperature in these containers and are easily purified without appreciable loss.]

- Degradation products and others

These are stored at -18 °C in the dark under argon in Teflon containers. They are generally more stable than CWAs and their precursor chemicals.

[Solutions of V-agent precursors $RO(Me)P(O)S^{-}Na^{+}$ in water (from their syntheses) store without appreciable decomposition; an aqueous solution (R = Et) declined in concentration from 1.4 to 1.2 mol/l over 13 years.]

One Designated Laboratory checks purities of stored Schedule 1 nerve and vesicant agents on a monthly basis because of uncertainties related to the stabilities of solutions upon storage. Reference standards are checked for purity before use. The ISO 17025 quality system requires purity checking of nominally stable chemicals, such as CWA degradation products, at least every two years.

2.2.2. Solutions of chemicals

Solutions of commercial chemicals used for laboratory standards are stored in clean glass containers (e.g. vials or volumetric flasks) under conditions specified in safety data sheets or the scientific literature. Dilute solutions of Scheduled chemicals in dichloromethane (10 ppm) are stable at ~4 °C in sealed ampoules/vials for 6 months (qualitative standards) or 12 months (qualitative standards) (Table 4). If the chemical or its container show signs of degradation, they should be disposed of safely.

Table 4. Designated Laboratory responses: solutions of chemicals.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks s	2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Commercial or synthesized, solution	General	refrigerator freezer (-18 °C) glass container Teflon lined caps in dichloromethane			■		■						■		■	
Commercial or synthesized, solution	Scheduled	refrigerator sealed									■					

Solutions of CWAs and degradation products used as standards are generally not stored for longer than 1 month in screw-capped vials in cases where sub-sampling of these solutions is a regular event. Nerve agents can be stored short-term in isopropanol and sulfur mustard in hexane. CWAs are stable in dichloromethane for a month, but their stability in this solvent has not been studied in detail.

The results of analysis suggest that CWAs absorbed onto painted surfaces [71] could be extracted and detected many years after dissemination, and studies have reported stability of CWAs on sorbent tubes for up to 1 month sufficient to permit identification [180].

2.2.3. Liquid (including extracts) and solid samples containing either relatively high levels or trace levels of the chemicals of interest and highly heterogeneous unprocessed samples – such as soil, metal fragments, paint chips, fragments of highly absorbent material, or wipes – containing either relatively high levels or trace levels of the chemicals of interest

Responses from the Designated Laboratories are summarised in Table 5. There is no evidence for long-term storage of solutions of CWAs used as standards beyond 6 months. However, anecdotal information suggests these types of samples can be stored for longer (years) at -18 °C. There is limited evidence that supports the storage of dilute (10 ng ml^{-1}) and concentrated (1 mg ml^{-1}) solutions of standards for at least 6 months [66,67].

Table 5. Designated Laboratory responses: samples in organic and aqueous solutions, solid/heterogeneous samples, and air samples.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks	2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Sample, organic solutions	General	refrigerator	■			■										
		freezer (-18 °C)	■					■			■					
		glass container	■			■										
		original container				■										
		sealed									■					
Sample, aqueous solutions	General	refrigerator	■			■					■					
		glass container	■			■										
		original container				■										
		PP container									■					
		sealed									■					
Sample, solid/heterogeneous	General	freezer (-18 °C)	■													
		refrigerator	■			■					■					
		glass container				■					■					
		HDPE container									■					
		original container				■										
		sealed									■					
Sample, air	General	refrigerator	■													
		freezer (-18 °C)	■													

Room temperature: usually 25 °C. PP : polypropylene. HDPE : High-density polyethylene.

GC-based techniques may lack long-term stability for repeat quantitative measurements for CWA solutions of concentration of 1 ng ml^{-1} and lower [66,67]. Solvent choice (quality, including water content) is likely to be of great importance as well as specific storage conditions, including how often solutions are used.

2.2.4. Biomedical samples: blood, plasma, urine, tissue

Designated Laboratories generally store these sample types at +4, -18 or -80 °C in glass, polypropylene or polyteraphthalate containers (Table 6). Estimates of maximum storage times

are matrix, analyte and concentration dependent; they range from months to years depending on storage conditions.

Little is known about the ageing of nerve agent blood adducts following long term storage. Sulfur mustard blood adducts, and urinary metabolites of sulfur mustard and nerve agents, have been re-analysed following several years of storage.

Table 6. Designated Laboratory responses: biomedical samples.

Chemical	Type	Storage Condition	Until assignment completed	Manufacturer recommendation	Until signs of degradation	Up to 2 weeks	Up to 1 month	Several months	Up to 3 months	Up to 6 months	Up to 1 year	Several years	Up to 3 years	Up to 5 years	More than 10 years
Biomedical samples	General	refrigerator				■				■					
		freezer (-18 °C)	■												
		freezer (-80 °C)										■			
		glass container				■				■					
		original container													
		sealed								■					
	Hair exposed to sarin	room temperature						■							
	Protein frozen	freezer (-18 °C)										■			
		freezer (-80 °C)										■			
	Protein lyophilized	freezer (-18 °C)										■			
		refrigerator										■			
	Protein in solution	refrigerator				■									
	Protein in solution with 50% glycerol	freezer (-18 °C)									■				
	Blood	freezer (-18 °C)								■					
		PET container								■					
		PP container								■					

Room temperature : usually 25°C. PET : polyethylene terephthalate. PP : polypropylene.

Detailed guidelines for storing and handling of protein-containing samples from one Designated Laboratory are provided in Supplementary Material, Appendix C [181].

2.2.5. Other technologies that could be used to store/package samples

Flame-sealed ampoules can be used to extend the storage stability of in-house reference chemicals. Certan® capillary bottles (LGC Group), available from Sigma-Aldrich Ltd., can be used to store highly-volatile samples. Solid phase microextraction fibres might be used to store nerve agent urinary metabolites for extended periods of time. Blood spot papers [223] and related technologies seem promising for long-term storage of blood and other biological matrices. Much of the perceived benefit is in the sampling aspects (less invasive, low volume) but there is also a range of direct mass spectrometric analysis technologies appearing on the market (for example, paper spray analysis [224]) that might prove valuable.

4. Conclusions

In the context of the OPCW's investigations, numerous samples have been received since 2013, which were, at the time this advice was given, stored in the OPCW Laboratory at room temperature or refrigerated at 4 °C. The SAB noted that these conditions may naturally lead to loss of the intact original chemicals by degradation, in, at worst, weeks to months, and at best, months to many years. The analysis of these samples thereafter may give results with less specific information, but still containing the molecular evidence, in the form of characteristic degradation compounds and other residues, for proving CWA use or making other compliance-related judgements. The main degradation of CWAs or other Convention-relevant chemicals in environmental samples occurs through hydrolysis and/or oxidation.

To minimise degradation of chemicals in the samples, as little time as possible should elapse from the time of collection of any sample to the time of analysis; lengthy delays of weeks to years will diminish the concentration of the intact original chemicals in the samples. Identification of the presence of the intact original chemical(s) is desirable, but not essential, for providing evidence of use of chemicals relevant to the Convention. Best-practice conditions for various samples summarised in Tables 1-6 have been used to make the recommendations provided in Section 2.

The OPCW should monitor advances in sampling and analysis, and with the SAB, innovations relevant to chemical forensics. Knowledge of storage conditions for CWAs and other Convention-relevant samples remains vital to the work of the OPCW in non-proliferation and the prevention of re-emergence of chemical weapons [3,4].

4. Afterword

Comments in this section were not part of the original SAB advice, but have been added in writing this review: As long as there is a possibility of the use, or threat of use, of chemical weapons, there will be a need to maintain and continually enhance the analytical capabilities of the OPCW. Such enhanced capabilities exert an important deterrent effect [4] and will help prevent the re-emergence of chemical weapons after completion of destruction of the declared stockpiles by the States Parties (at the beginning of 2018, this stood at more than 96% of the over 70,000 metric tonnes declared by States Parties having been verifiably destroyed [225]). Such re-emergence could manifest itself through the acquisition and/or use of chemical weapons, including by non-State actors [226]. It is essential that the OPCW has available state-of-the-art methods and technologies for sampling and analysis at its disposal, ensures that staff are kept abreast of and trained in these, and actively develops capabilities in chemical forensics, incorporating advice from the SAB and in consultation with the network of Designated Laboratories, including for the analysis of toxins as well as biomedical and other samples [226].

To assist in these efforts, the Finnish Institute for Verification of the Chemical Weapons Convention (VERIFIN) hosted a SAB Workshop on Chemical Forensics in Helsinki in June 2016 [227]. As an outcome of this workshop, the OPCW Director-General requested the SAB to form a Temporary Working Group (TWG) on Investigative Science and Technology [228] which held its first meeting in February 2018 [229]. An objective of this TWG is 'to review the science and technology relevant to investigative work, especially for the validation and provenancing (determining the chronology of ownership, custody and/or location) of evidence, and the integration of multiple and diverse inputs to reconstruct a past event' [228-230]. This TWG will influence the next stage of the development of analytical and forensic capabilities of the OPCW and its partner laboratories [231,232]. A newly established Chemical Forensics International Technical Working Group [233] will also support such work.

Acknowledgements

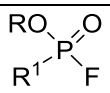
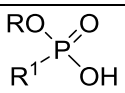
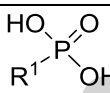
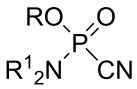
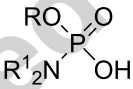
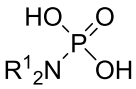
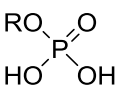
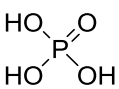
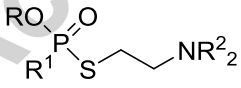
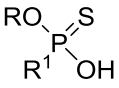
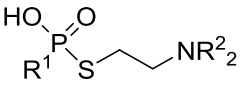
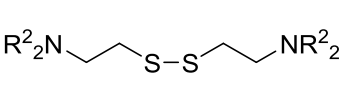
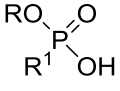
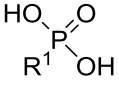
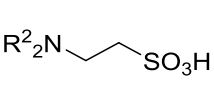
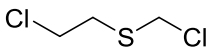
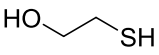
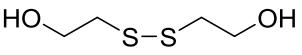
The SAB wishes to thank His Excellency Ambassador Ahmet Üzümcü, Director-General of the OPCW, for his support to the Board and for making its output available to States Parties to the Convention to guide their decision-making. The SAB extends its gratitude to Dr. James

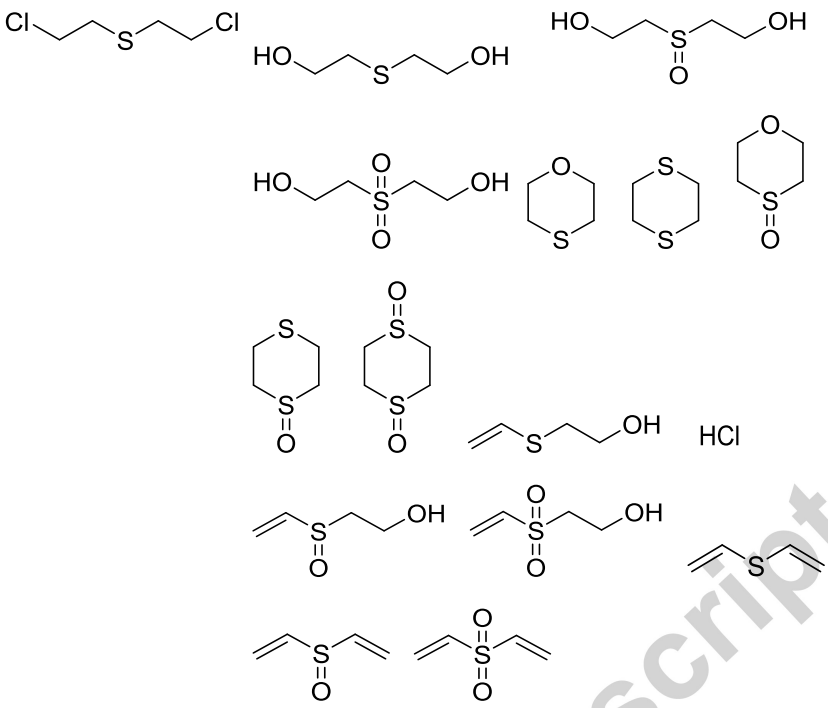
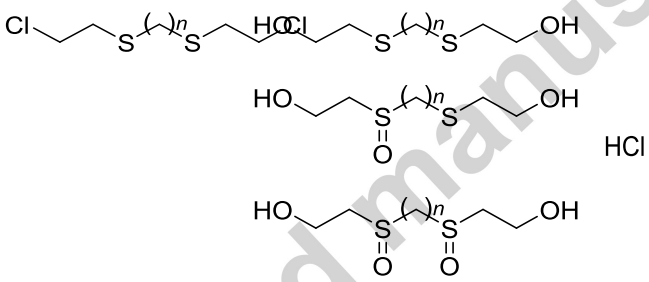
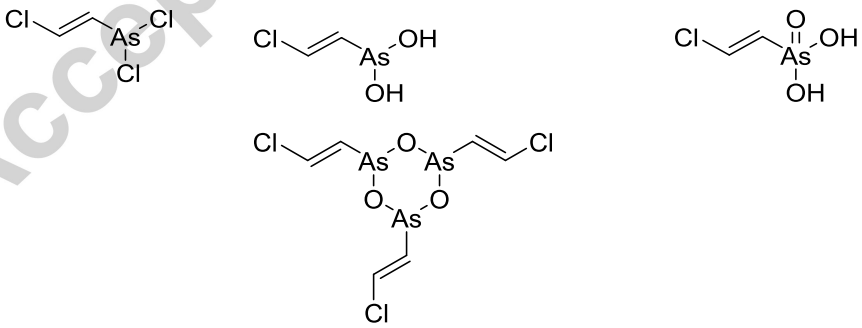
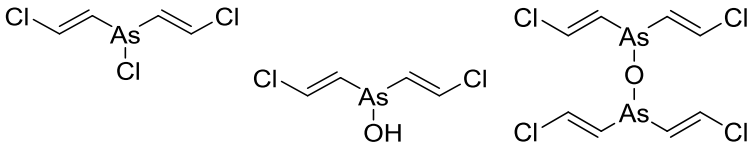
Riches, Mr. Robert Read, and Mr. Mark Sandford of the Defence Science and Technology Laboratory (Dstl), Porton Down, UK, for information relating to the analysis and storage of CWAs, and to Mr. Zaid Meherali of Dstl, for helping prepare the questionnaire that was sent to the OPCW Designated Laboratories. The SAB is grateful to the personnel of those laboratories that completed the questionnaires and shared their expert opinion, and also to Ms. Marlene Payva for her skilful assistance to the Board.

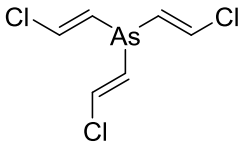
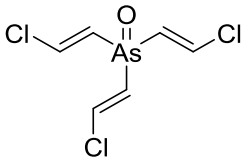
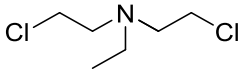
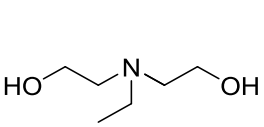
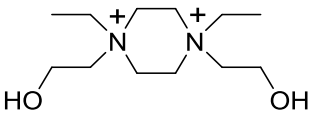
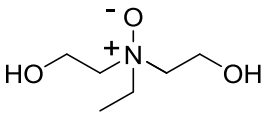
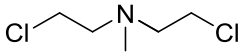
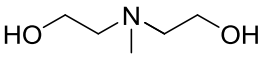
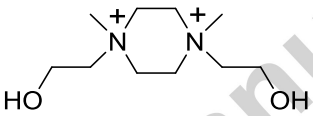
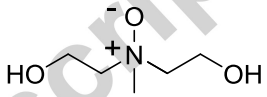
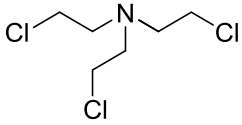
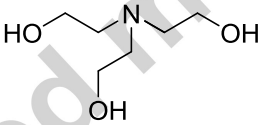
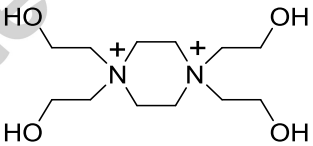
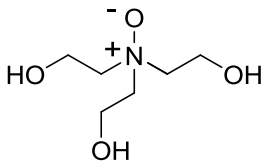
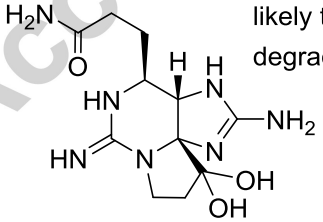
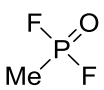
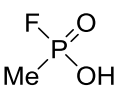
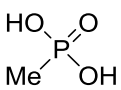
Declarations of interest

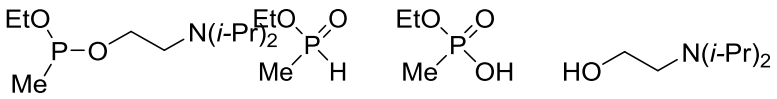
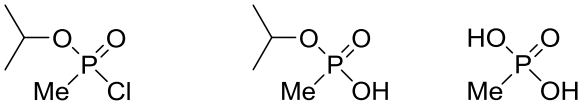
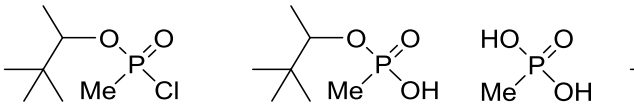
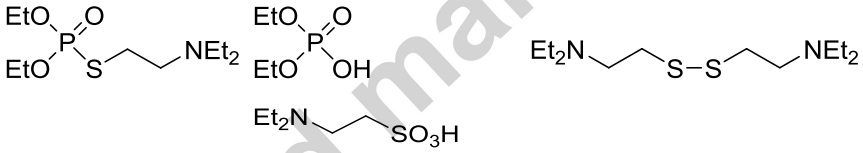
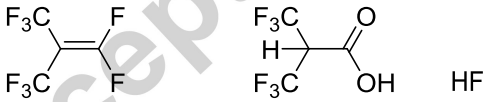
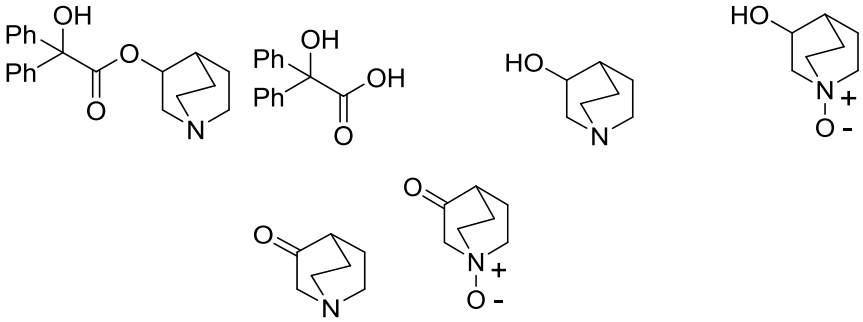
None.

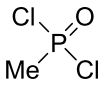
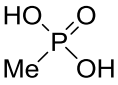
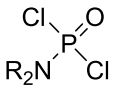
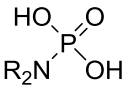
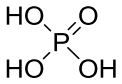
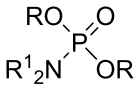
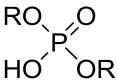
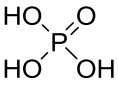
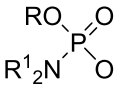
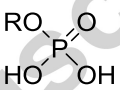
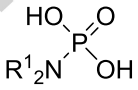
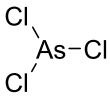
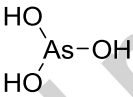
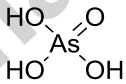
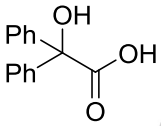
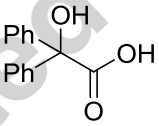
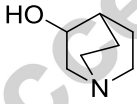
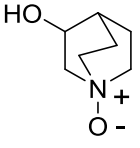
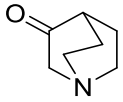
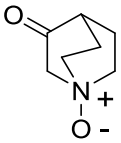
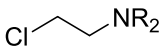
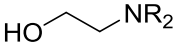
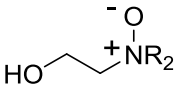
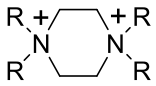
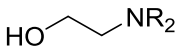
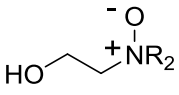
Appendix. Scheduled chemicals and major degradation products identified from the scientific literature.

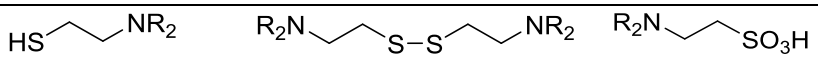
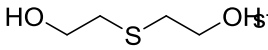
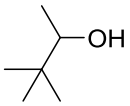
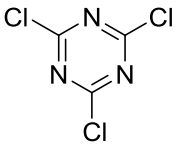
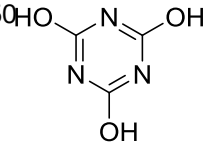
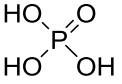
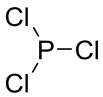
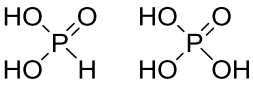
SCHEDULE	STRUCTURE	MAIN DEGRADATION PRODUCTS	REF/S
Schedule 1.A.01 *O*-Alkyl alkylphosphonofluoridates (e.g. sarin, soman)		  HF	42,51,71, 182,183
Schedule 1.A.02 *O*-Alkyl *N*,*N*-dialkyl phosphoramidocyanidates (e.g. tabun)		    HCN	42,51,184
Schedule 1.A.03 *O*-Alkyl *S*-2-dialkylaminoethyl alkylphosphonothiolates (e.g. VX)		     	42,51,184-193
Schedule 1.A.04 Sulfur mustards 2-Chloroethylchloro		  HCHO	184

methyl-sulfide	HCO_2H HCl	
Bis(2-chloroethyl)sulfide (mustard gas, HD)		40,194-197
Bis(2-chloroethylthio)alkanes (“Heavy mustards”, *n* = 1 to 5)	 HCl	195
Schedule 1.A.05 Lewisites		
2-Chlorovinyldichloroarsine (Lewisite 1)		198-205
Bis(2-chlorovinyl)chloroarsine (Lewisite 2)		198-205

Tris(2-chlorovinyl)arsine (Lewisite 3)		usually does not degrade, but can oxidise to this		198-205
Schedule 1.A.06 Nitrogen mustards				
Bis(2-chloroethyl)ethylamine (HN-1)		 		49,50,206
Bis(2-chloroethyl)methylamine (HN-2)		 		49,50
Tris(2-chloroethyl)amine (HN-3)		 		49,50,206
Schedule 1.A.7 Saxitoxin		likely to remain intact - the possible degradation products are unknown		207
Schedule 1.A.8 Ricin	complex protein	likely to denature - the possible degradation products are unknown		208-210
Schedule 1.B Precursors				
Schedule 1.B.09 Alkylphosphonic		 	HF	51

difluorides (e.g. DF)		
Schedule 1.B.10 *O*-Alkyl *O*-2-dialkylaminoethyl alkylphosphonites (e.g. QL)		51
Schedule 1.B.11 *O*-Isopropyl methylphosphono - chloridate (chlorosarin)		51
Schedule 1.B.11 *O*-Pinacolyl methylphosphono - chloridate (chlorosoman)		51
Schedule 2		
A. Toxic chemicals		
Schedule 2.A.01 *O*,*O*-Diethyl *S*-[2-(diethylamino)ethyl] phosphorothiolate (Amiton)		51
Schedule 2.A.02 1,1,3,3,3-Pentafluoro-2-(trifluoromethyl)-1-propene (PFIB)	 HF	184,211-213
Schedule 2.A.03 3-Quinuclidinyl benzilate (BZ)		214
Schedule 2.B.04		

Chemicals, except those listed in Schedule 1 containing a phosphorus atom to which is bonded one methyl, ethyl or propyl (*n* or *iso*) group but no further carbon atoms	For example, methyl-phosphonic dichloride (DC) 		HCl		51,211, 215
Schedule 2.B.05 *N*,*N*-Dialkylphosphoramidic dihalides				HCl	51
Schedule 2.B.06 Dialkyl *N*,*N*-dialkylphosphoramidates		 		 	51
Schedule 2.B.07 Arsenic trichloride				HCl	49,50
Schedule 2.B.08 2,2-Diphenyl-2-hydroxyacetic acid			generally will not degrade any further		184,214
Schedule 2.B.09 Quinuclidin-3-ol					184,214
Schedule 2.B.10 *N*,*N*-Dialkylaminoethyl-2-chlorides					216
Schedule 2.B.11 *N*,*N*-Dialkylaminoethane-2-ols		generally will not degrade further			216

Schedule 2.B.12 *N*,*N*-Dialkylaminoethane-2-thiols			186
Schedule 2.B.13 Bis(2-hydroxyethyl)sulfide (thiodiglycol)		stable in the environment can oxidise to the sulfoxide and sulfone (degradation products of sulfur mustard)	71,184, 194-197
Schedule 2.B.14 3,3-Dimethylbutan-2-ol (pinacolyl alcohol)		stable in the environment (degradation product of soman)	217
Schedule 3			
A. Toxic chemicals			
Schedule 3.A.01 Carbonyl dichloride (phosgene)		non-persistent, hydrolysing with ease to HCl and CO_2	212,218
Schedule 3.A.02 Cyanogen chloride	ClCN	only slightly soluble in H_2O; polymerises to  which hydrolyses to give this triol 	49,50
Schedule 3.A.03 Hydrogen cyanide	HCN	persists in the open for only a few minutes after release - acid hydrolyses it to $HCONH_2$	219,220
Schedule 3.A.04 Trichloronitromethane (chloropicrin)	CCl_3NO_2	stable in the environment	49,50
B. Precursors			
Schedule 3.B.05 Phosphorus oxychloride		 HCl	51
Schedule 3.B.06 Phosphorus trichloride		 HCl	51

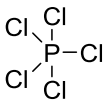
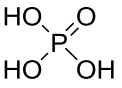
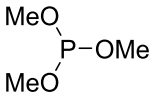
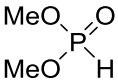
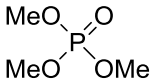
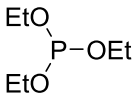
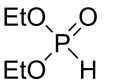
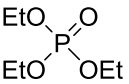
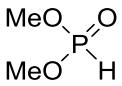
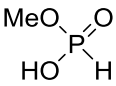
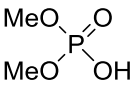
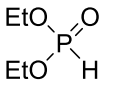
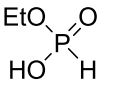
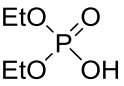
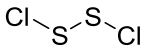
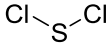
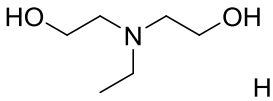
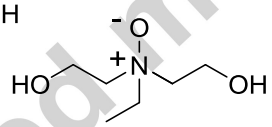
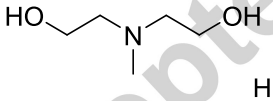
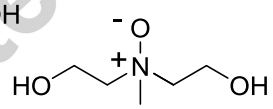
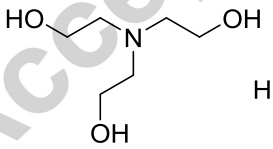
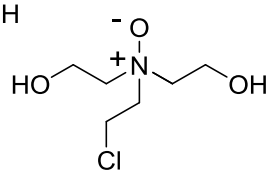
Schedule 3.B.07 Phosphorus pentachloride		 HCl	51
Schedule 3.B.08 Trimethyl phosphite		 	51
Schedule 3.B.09 Triethyl phosphite		 	51
Schedule 3.B.10 Dimethyl phosphite		 	51
Schedule 3.B.11 Diethyl phosphite		 	51
Schedule 3.B.12 Sulfur monochloride		sulfur HCl H_2SO_3	222
Schedule 3.B.13 Sulfur dichloride		sulfur HCl H_2SO_3	-
Schedule 3.B.14 Thionyl chloride		HCl SO_2 H_2O	-
Schedule 3.B.15 Ethyldiethanolamine			222
Schedule 3.B.16 Methyldiethanolamine			222
Schedule 3.B.17 Triethanolamine			222

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Figure 1. OPCW Designated Laboratory network in January 2018 showing labs designated for environmental (E) and/or biomedical (B) sample analysis.

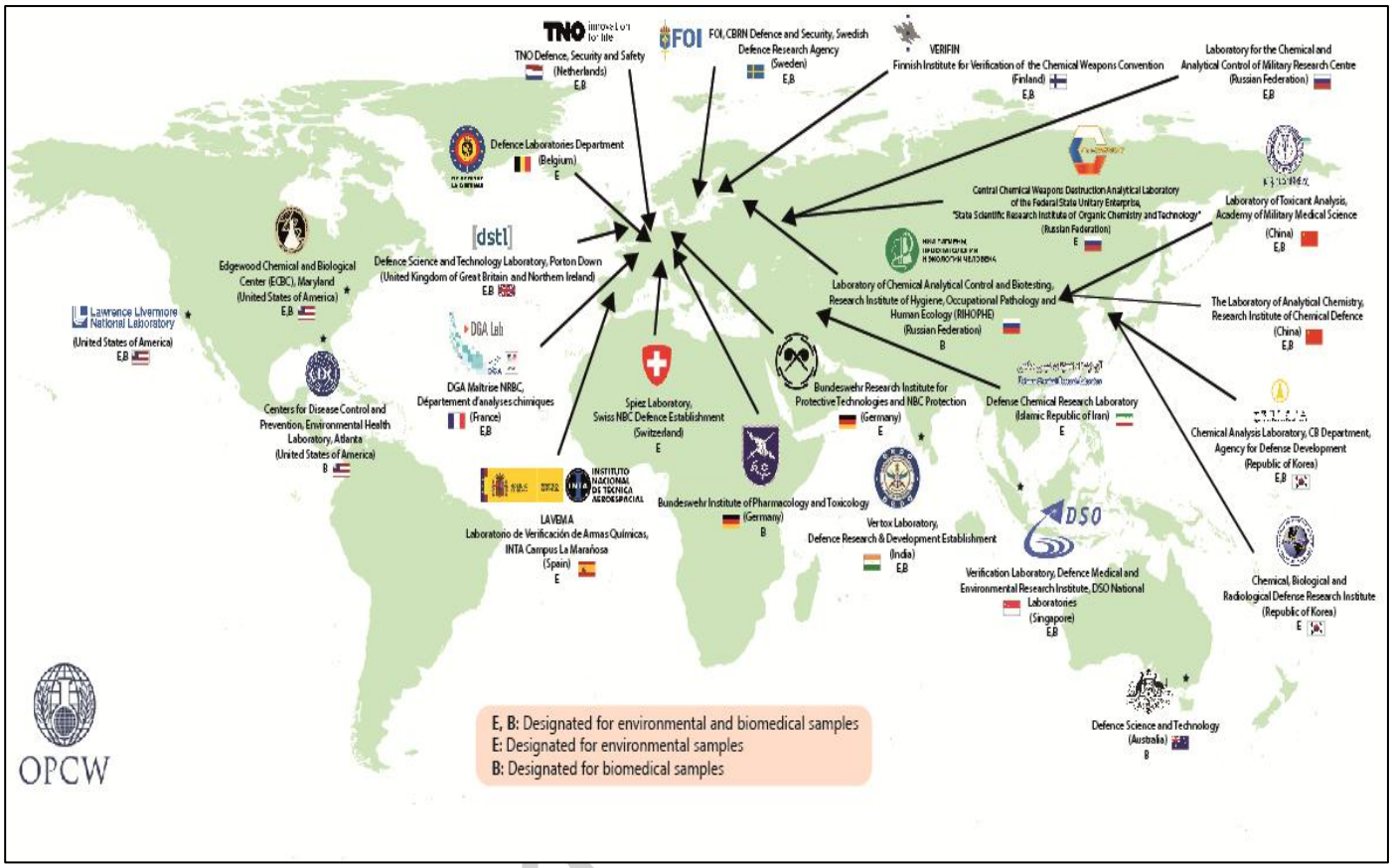

Figure 2. SAB Vice-Chair Mr. Cheng Tang (*left*) and SAB Chair Dr. Christopher Timperley (*middle*) briefing the OPCW Director-General, His Excellency Ahmet Üzümcü (*right*), on the sample storage and stability advice given herein, at the OPCW Headquarters in The Hague in 2016.

Figure 3. OPCW SAB with the Director-General at the Twenty-Third Session of the Board on 22 April 2016. The SAB endorsed the report containing the advice on CWA sample storage and stability during this session.

Highlights

- The Scientific Advisory Board (SAB) of the Organisation for the Prohibition of Chemical Weapons (OPCW) considered the long-term storage and stability of samples collected in the context of chemical weapons investigations.
- The resulting advice, useful for all laboratories that conduct analysis on samples containing chemical warfare agents, their precursors and/or degradation products, is described.

- The scientific literature on environmental and biomedical sample analysis, and the main degradation products for chemicals on the Schedules in the Annex on Chemicals of the Chemical Weapons Convention, is reviewed.
- Ten recommendations to ensure the long-term storage and stability of samples collected in relation to the potential use of chemical weapons are provided.