Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction

10 August 2018

English only

2018 Meeting
Geneva, 4-7 December 2018

Meeting of Experts on Review of developments in the field of science and technology related to the Convention
Geneva, 9-10 August 2018
Item 8 of the provisional agenda
Any other science and technology developments of relevance to the Convention and also to the activities of relevant multilateral organizations such as the World Health Organization (WHO), World Organisation for Animal Health (OIE), Food and Agriculture Organization (FAO), Intergovernmental Panel on Climate Change (IPPC) and Organisation for the Prohibition of Chemical Weapons (OPCW)

Report of the Scientific Advisory Board of the Organisation for the Prohibition of Chemical Weapons on Developments in Science and Technology for the Fourth Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention

Note by the Implementation Support Unit*

1. In its final report, the Meeting of States Parties to the Biological Weapons Convention in December 2017 included the following item to be considered by the Meeting of Experts on Review of Developments in the Field of Science and Technology Related to the Convention: “Any other science and technology developments of relevance to the Convention and also to the activities of relevant multilateral organizations such as the WHO, OIE, FAO, IPPC and OPCW”.

2. The OPCW has applied to participate in the 2018 Meeting of Experts on Review of Developments in the Field of Science and Technology Related to the Convention and has submitted the attached report (see the annex) dated 30 April 2018 which is reproduced here as submitted, without formal editing and with the original pagination.

* The Arabic, Chinese, French, Russian and Spanish versions of this document are available from the OPCW.

OPCW

Review Conference

Fourth Session
21 – 30 November 2018

RC-4/DG.1
30 April 2018
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REPORT OF THE SCIENTIFIC ADVISORY BOARD ON DEVELOPMENTS IN SCIENCE AND TECHNOLOGY FOR THE FOURTH SPECIAL SESSION OF THE CONFERENCE OF THE STATES PARTIES TO REVIEW THE OPERATION OF THE CHEMICAL WEAPONS CONVENTION

Introduction

1. The Scientific Advisory Board (SAB) was established by the Director-General in accordance with subparagraph 21(h) and paragraph 45 of Article VIII of the Chemical Weapons Convention (hereinafter "the Convention"), so that he could render to the Conference of the States Parties (hereinafter "the Conference") and the Executive Council (hereinafter "the Council") specialised advice in areas of science and technology relevant to the Convention. In keeping with this mandate, and as its contribution to the Fourth Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention (hereinafter "the Fourth Review Conference"), to be held from 21 to 30 November 2018, the SAB has prepared this report, which analyses relevant developments in science and technology over the past five years and presents recommendations and observations that the SAB considers to be important for the review of the operation of the Convention and its future implementation.

2. This report contains an executive summary and recommendations addressing issues that may impact the implementation of the Convention and the work of the Technical Secretariat (hereinafter "the Secretariat"). The analysis of developments in science and technology that informed the recommendations, as well as additional, more detailed recommendations, are provided in Annex 1.

3. This is the fourth report for a Review Conference by the SAB on developments in science and technology relevant to the Convention. The three earlier reports were presented to the First Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention[1] (hereinafter "the First Review Conference"), the Second Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention[2] (hereinafter "the Second Review Conference"), and the Third Special Session of the Conference

[1] RC-1/DG.2, dated 23 April 2003.
[2] RC-2/DG.1, dated 28 February 2008 and Corr.1, dated 5 March 2008.

of the States Parties to Review the Operation of the Chemical Weapons Convention[3] (hereinafter "the Third Review Conference").

4. To guide the scientific review, the SAB has drawn insights from sources that include:

(a) its three earlier reports to the First, Second, and Third Review Conferences;

(b) the deliberations of the SAB during regular Sessions of the Board since the Third Review Conference (documented in the reports from the Twentieth to Twenty-Seventh Sessions);[4]

(c) the deliberations of the SAB's temporary working groups (TWG) on the convergence of chemistry and biology[5] (from November 2011 to November 2013), education and outreach[6] (from November 2012 to September 2014), verification[7] (from March 2013 to May 2015), and investigative science and technology, which held its first meeting prior to the publication of this report;[8]

(d) a series of four workshops,[9] co-organised by the SAB and external partners and kindly funded by the European Union. These addressed chemical forensics (held in Helsinki, Finland, in June 2016), medical countermeasures and emergency response (held in Paris, France, in September 2016), emerging technologies (held in Rio de Janeiro, Brazil, in July 2017), and trends in chemical production (held in Zagreb, Republic of Croatia, in October 2017);

(e) intersessional responses from the SAB to five requests for advice by the Director-General from 2013 to 2017. These requests considered medical countermeasures and longer term treatment for victims of chemical agent

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3 RC-3/DG.1, dated 29 October 2012.

4 SAB-20/1, dated 14 June 2013; SAB-21/1, dated 27 June 2017; SAB-22/1, dated 21 July 2017; SAB-23/1, dated 22 April 2016; SAB-24/1, dated 28 October 2016; SAB-25/1*, dated 31 Mach 2017; SAB-26/1, dated 20 October 2017; and SAB-27/1, dated 23 March 2018.

5 The final report of the TWG on Convergence of Chemistry and Biology was published as SAB/REP/1/14, dated June 2014. Available at: www.opcw.org/fileadmin/OPCW/SAB/en/TWG_Scientific_Advsiory_Group_Final_Report.pdf. A quick reference guide to its recommendations is available at: www.opcw.org/fileadmin/OPCW/SAB/en/Convergence_of_Chemistry_and_Biology_1-01.pdf.

6 The final report of the TWG on Education and Outreach was published as SAB/REP/2/14, dated 28 November 2014. Available at: www.opcw.org/fileadmin/OPCW/SAB/en/Education_and_Engagement-v2.pdf.

7 The final report of the TWG on Verification was published as SAB/REP/1/15, dated June 2015. Available at: www.opcw.org/fileadmin/OPCW/SAB/en/Final_Report_of_SAB_TWG_on_Verification_-_as_presented_to_SAB.pdf. A quick reference guide to its recommendations is available at: www.opcw.org/fileadmin/OPCW/SAB/en/VER_Poster_5102015.pdf.

8 SAB-27/WP.1, dated 26 February 2018.

9 See: SAB-24/WP.1, dated 14 July 2016, SAB-26/WP.1, dated 21 July 2017, and SAB-26/WP.2, dated 19 October 2017.

exposure,[10] isotopic labels and stereochemistry of scheduled chemicals,[11] sample storage and stability,[12] and riot control agents;[13]

(f) the participation of members of the SAB in scientific conferences and workshops, including Spiez CONVERGENCE workshops held in 2014 and 2016,[14] and engagement with other scientific advisory mechanisms;

(g) a range of scientific literature and patents across diverse areas of relevance; and

(h) the individual expertise of the members of the Board who have contributed equally to the scientific review process.

5. With regard to subparagraphs 3(b) to (e) above, 27 meetings and workshops were held with a combined participation of 747 (289 individuals from 58 States Parties), 32 reports were produced, and 453 presentations and briefings were received (from 201 individual speakers). A complete list of reports and related documents is provided in Annex 2.

6. The SAB notes that science and technology directly inform key articles of the Convention, ranging from those that define a chemical weapon through to those ensuring the completeness of declarations, the application of sampling and analysis and other verification methodologies, the processes for inspections and investigations, and the requirements of destruction technologies, as well as the articles governing assistance, protection, and outreach to scientific communities. Furthermore, the Board highlights that we are fortunate to be living in an era of unprecedented scientific advancement and technological innovation with equally unprecedented access to, and diffusion of, scientific knowledge. As the dynamism of science can both improve and potentially undermine the ability to maintain an effective disarmament regime, the SAB emphasises that disarmament cannot afford to be scientifically illiterate.

7. The science of chemistry has experienced continual change throughout its history and today we are seeing the emergence and practical applications of new and innovative technologies, as well as the repurposing of existing technologies for unanticipated new applications relevant to chemistry. Technological change benefits from increasingly transdisciplinary and convergent approaches to problem solving and technology development across scientific communities. This convergence across traditional disciplinary boundaries fuels the rapid pace of developments in science and technology that is often discussed within chemical and biological security communities.

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10 See: SAB-21/WP.7, dated 29 April 2014; and SAB-22/WP.2/Rev.1, dated 10 June 2015.

11 See: SAB-23/WP.1, dated 28 April 2016.

12 See: SAB-23/WP.2, dated 25 May 2016.

13 See: SAB-25/WP.1, dated 27 March 2017.

14 See: Spiez CONVERGENCE: Report of the First Workshop, 2014, available at: https://www.labor-spiez.ch/pdf/de/rue/Spiez_Convergence_2014_web.pdf, and Spiez CONVERGENCE: Report of the Second Workshop, 2016, available at: https://www.labor-spiez.ch/pdf/en/rue/LaborSpiezConvergence2016_02_FINAL.pdf.

8. With new advances across the chemical sciences increasingly being enabled by ideas and tools originating from sectors outside the traditional realm of chemistry (as well as enabling advances in other disciplines), Convention-relevant developments in science and technology may not be easily recognised if the scientific review process is restrained to chemical-specific fora. There is also a need for practical considerations to ensure that the review recognises opportunities made available through innovative approaches to technology development and application.

EXECUTIVE SUMMARY

Developments that may impact the scope of the implementation of the Convention

9. The number of new chemicals reported in scientific literature continues to rapidly expand. The broad scope of the provisions of the Convention ensures that new chemicals are covered under its terms.

10. While the field of chemistry continued to report steady advances over the five years since the report to the Third Review Conference, some more important developments in science and technology relevant to the Convention occurred across disciplinary boundaries, the understanding of the chemistry of life processes being one of the most pertinent examples. These developments were facilitated by rapid advances in technologies for genome editing, gene synthesis, and gene sequencing. Taken together, these advances have enabled remarkable progress in understanding the functioning of life processes at the molecular level. With this greater understanding also comes a greater ability to manipulate—and to interfere with—life processes. The SAB expects capabilities in these areas to continue to grow for the foreseeable future.

11. The rapid advances in the life sciences have the potential to significantly impact the chemical industry. Biological and/or biologically-mediated processes have been upscaled for industrial chemical production capable of producing organic chemicals in quantities that should make them declarable under the terms of the Convention. To date, such processes do not appear suitable or offer any advantages for the production of traditional chemical warfare agents (CWA). However, toxins and materials of biological origin are amenable to such methods. The SAB notes that one of the most active industrial areas for adoption of biological or biomediated methods is the specialty chemical sector, which includes a number of types of chemical- and biological- based pharmaceuticals.

12. Over the last five years, the importance of chemical safety and security has been increasingly recognised among States Parties and at the OPCW, particularly in light of the confirmed use of chemical weapons by non-State actors. International efforts to strengthen chemical safety and security draw heavily upon science and technology, including modelling, risk assessment, risk mitigation, and the development of production processes that reduce or minimise the presence of highly toxic chemicals.

13. The emergence and practical application of new and innovative technologies, as well as the re-purposing of existing technologies for unanticipated new applications, is leading to increasingly transdisciplinary approaches to problem solving and technology development. Advances in fields such as remote sensing, data mining and the analysis of very large amounts of data, artificial intelligence, forensic science, and

automated and autonomous systems can be utilised to increase the OPCW's capability to verify compliance. In order to seize opportunities that could benefit the implementation of the Convention, it is important to engage with relevant communities of experts.

Developments related to the Technical Secretariat

14. The broad and rapid advances in scientific and technical fields relevant to the implementation of the Convention increase the importance for the Secretariat to maintain and grow its capability to monitor developments and assess their impact. Not only is the role of the Science Policy Advisor increasingly important, but the challenge of maintaining a broad and strong technical foundation for the Secretariat's activities, including an experienced and technically knowledgeable cadre of verification experts and inspectors, has also grown.

15. As noted in the SAB's report to the Third Review Conference, developments in production technologies and the ensuing changes in the chemical industry will necessitate that the Secretariat enhance its technical knowledge of those areas. More broadly, enhanced training, increased interaction with outside experts, and other professional development efforts will be important in helping to ensure that the expertise within the Secretariat keeps pace with outside developments.

RECOMMENDATIONS

Advice on advances in science and technology

16. Given the potential impact on the Convention of the convergence of chemistry and biology, the SAB and Secretariat should keep under review developments in biological and biomediated processes, metabolic engineering, the synthesis of replicating organisms, the use of enzymes for decontamination, and biotechnology, as well as any other related aspects it deems relevant to the Convention, and report on their implications for the Convention. *For further consideration, see paragraphs 1 to 33 and 135 to 143 of Annex 1.*

17. The SAB and the Secretariat should continue to work across areas of overlap between the Chemical Weapons Convention and the Biological Weapons Convention and promote joint discussions amongst international experts in these areas. *Relevant areas of overlap can be found throughout Annex 1 (in particular, paragraphs 1 to 75, 97 to 119, 135 to 143 and 204 to 211).*

18. The SAB and Secretariat should continue to assess developments in technical fields of increasing relevance to the Convention, such as computational chemistry, Big Data, informatics and artificial intelligence, forensic science, remote sensing, and unmanned automated systems. *For further consideration, see paragraphs 63 to 75 of Annex 1.*

19. Although biological or biomediated processes do not currently appear likely to be suitable for production of traditional chemical warfare agents, the Secretariat should continue to monitor developments closely. *For further consideration, see paragraphs 4 to 9, 13 to 16, 24 to 33 and 139 to 143 of Annex 1.*

20. The SAB continues to emphasise the recommendation that, taking into consideration the convergence of chemistry and biology as it relates to the synthesis of chemicals, any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis". *For further consideration, see paragraph 5 of Annex 1.*

21. As the number and variety of facilities using a biological or biomediated process to produce chemicals increase, the degree of relevance of these facilities to the object and purpose of the Convention will need to be assessed to determine whether there are grounds to exempt certain types of facilities or a need to review thresholds for declaration and inspection of other chemical production facilities (OCPFs). *For further consideration, see paragraphs 122 to 134 of Annex 1.*

22. In view of the many interesting and potentially enabling technologies that are described in this report, the Secretariat is encouraged to consider ways in which such technologies may prove valuable in enhancing its capability to verify compliance with the Convention and to assist States Parties in improving their own capabilities. This should be informed by capability requirements, not the technology itself. In general, the SAB is of the view that technological change is best considered from a practical perspective, focusing on capabilities relevant to the Convention, irrespective of scientific discipline. *For further consideration, see paragraphs 339 to 344 and 349 to 350 of Annex 1.*

23. The SAB recommends that the Secretariat adopt a systematic approach to the continued professional development of its technical experts to ensure that they possess the knowledge and expertise to identify, evaluate, and apply scientific and technological advances relevant to its work. *For further consideration, see paragraphs 128 to 131, 133 and 348 to 349 of Annex 1.*

Advice on chemicals

24. Given the substantial changes in chemistry and chemical industry since the schedules were finalised a quarter century ago, a review of the schedules should be considered to assess whether: (a) the chemicals currently listed are in the appropriate schedule, and (b) any toxic chemicals or specific precursors should be added to or removed from the schedules. In this connection, it should be considered whether it is technically feasible to accurately monitor Schedule III chemicals that are produced in very large quantities (e.g. over 100,000 tons/year). *For further consideration, see paragraphs 76 to 121 and 131 of Annex 1.*

25. The SAB advises against relying solely upon Chemical Abstracts Service (CAS) numbers to define chemicals covered by the schedules. Although relevant as aids to declaration and verification, CAS numbers are not the only means to identify a chemical or to determine whether a chemical is included in or excluded from a schedule. This advice is consistent with previous SAB views on this subject. *For further consideration, see paragraphs 82, 90, and 92 of Annex 1.*

26. In order to ensure the consistency of declarations, if a chemical is included within a schedule, then all possible isotopically-labelled forms and stereoisomers of that chemical should be included, irrespective of whether or not they have been assigned a CAS number or have CAS numbers different to those shown in the Annex on

Chemicals to the Convention. The isotopically-labelled compound or stereoisomer related to the parent chemical specified in the schedule should be interpreted as belonging to the same schedule. *For further consideration, see paragraphs 81 to 92 of Annex 1.*

27. Technical discussions of so-called "incapacitating chemicals" or central nervous system-acting (CNS) chemicals remain exhausted. The SAB sees no value in revisiting this topic as scientific facts remain unchanged since the SAB first considered the issue. In view of the increasing availability of such chemicals, the Secretariat should be prepared to develop capabilities that could be required to conduct missions involving an alleged use of CNS-acting chemicals for hostile purposes, including sample collection and the addition of analytical data to the OPCW Central Analytical Database (OCAD). This is consistent with previous SAB advice on the subject. *For further consideration, see paragraphs 97 to 101 and 224 to 226 of Annex 1.*

28. In view of the use of toxic industrial chemicals (TICs) as chemical weapons, the Technical Secretariat should seek to identify markers that may be formed through reactions of TICs with living tissue or materials present in the environment and assess the utility of such markers in investigations. *For further consideration, see paragraphs 102 to104, 224 to 226, and 229 to 232 of Annex 1.*

29. The Secretariat should enhance its efforts to strengthen the capabilities of international laboratories to identify the hostile use of toxins and analyse samples for toxins. This could include: (a) updating the existing ricin and saxitoxin fact sheets; (b) preparing similar fact sheets on other toxins that have been weaponised (such as staphyloccal enterotoxin B) or that are deemed to pose a high risk of potential use as weapons; (c) identifying a priority set of toxins for the development of analytical methods; and (d) collaborating closely with other networks of laboratories that are seeking to build capabilities for toxin analysis. *For further consideration, see paragraphs 105 to 116 of Annex 1.*

Advice on developments in chemical production and chemical discovery

30. OPCW verification could benefit from risk assessment tools and practices employed in the chemical industry, specifically those that have been developed to facilitate safer process and product design, and for regulatory compliance. *For further consideration, see paragraphs 122 to 134 of Annex 1.*

31. Aspects of good practices employed in the chemical industry for knowledge management could enable more efficient use of information in OPCW operations. *For further consideration, see paragraph 127 of Annex 1.*

32. Efforts to ensure that the verification regime remains effective would benefit from more extensive engagement with technical experts from industry, and review of industry-focused research and development, including the driving forces for adoption of new technologies into industrial processes. *For further consideration, see paragraphs 128 to 131 and 133 of Annex 1.*

33. Many facilities worldwide produce toxic chemicals that may be relevant to the Convention in quantities below current declaration thresholds (e.g. highly active

pharmaceutical ingredients or toxins used for cosmetic purposes or cancer therapy). The corresponding verification thresholds for facilities producing such chemicals should be addressed by the SAB and its recommendations should be considered. *For further consideration, see paragraphs 126 and 132 of Annex 1.*

Advice on technologies for the delivery of toxic chemicals and drugs

34. The continued development of unmanned aerial vehicles (UAVs) to deliver payloads for permitted purposes should be monitored to assess risks of development for chemical weapon delivery purposes. *For further consideration, see paragraphs 152 and 154 of Annex 1.*

Advice on science and technology of relevance to verification

35. Effective verification requires assessment of all relevant information pertaining to a site and the State Party, not simply the evaluation of a single inspection. Consequently, the Secretariat should move toward an integrated approach where all of the separate elements of information are combined and analysed systematically. *For further consideration, see paragraphs 161 to 167 of Annex 1.*

36. In order to enable the Secretariat to take a more analytical approach to verification, using all available information, the Secretariat should review the Verification Information System (VIS), develop new templates for Article VI inspection reports that would make it possible to upload the entire report to the VIS as a searchable document and explore possibilities for the secure transmission of documents and data between an inspection site and OPCW Headquarters. *For further consideration, see paragraphs 161 to 167 of Annex 1.*

37. The SAB notes that satellite imagery has proven useful in planning contingency operations and recommends that the Secretariat consider cooperating with other international organisations and experts to enhance its capability to interpret and apply satellite information to non-routine operations. The use of hyperspectral, thermal, and near-infrared imagery can provide information related to chemical changes in the imaged area. *For further consideration, see paragraphs 165, 194 to 203, 228 and 235 to 236 of Annex 1.*

38. In order to enable inspection teams to operate in dangerous or remote areas, the Secretariat should review remote and automated monitoring technologies to identify where their capabilities could be beneficial. Corresponding equipment should be added to the list of approved inspection equipment. *For further consideration, see paragraphs 194 to 223 of Annex 1.*

39. Appropriate analytical data for chemicals that may pose a risk to the Convention or that are needed to help differentiate permitted activities from prohibited activities should be added to the OCAD. This could include isotopically-labelled relatives and stereoisomers of scheduled compounds, salts of scheduled chemicals, toxic industrial chemicals, CNS-acting chemicals, riot control chemicals, bioregulators, toxins, and unscheduled chemicals that have been identified as posing a risk to the Convention. *For further consideration, see paragraphs 224 to 226 and 255 of Annex 1.*

40. In order to strengthen the capability of the designated laboratory network to analyse operational samples, the SAB recommends that preparedness to do so be a factor in maintaining designation and that the network be expanded both geographically and in terms of capabilities. *For further consideration, see paragraphs 227 and 249 to 253 of Annex 1.*

41. The SAB recommends that technical data related to sample analyses conducted for the OPCW be shared among laboratories in the network and published in peer-reviewed scientific journals, enabling all laboratories to benefit from proven methods and technologies. *For further consideration, see paragraph 252 of Annex 1.*

42. Given the requirement for the OPCW to be able to investigate alleged use of non-scheduled toxic chemicals, the capability to detect and identify traces of such chemicals and associated degradation and reaction products should be strengthened, inter alia, through suitable exercises. *For further consideration, see paragraphs 185 to 193 and 227 to 235 of Annex 1.*

43. In view of the critical role of biomedical samples in investigations of alleged use of toxic chemicals, the Secretariat should actively encourage further research on potential markers of exposure to such chemicals. The Secretariat should engage with experts from a broad range of fields to identify promising analytical approaches. *For further consideration, see paragraphs 241 to 261 of Annex 1.*

44. In order to facilitate investigations of alleged prohibited activities, the Secretariat should maintain a curated collection of reference samples and chemical data, including compiled data on abandoned chemical weapons, the environmental fate of toxic chemicals, and impurities associated with synthetic routes to nerve and blister agents. *For further consideration, see paragraphs 236 to 239, 279 to 281 and 287 to 288 of Annex 1.*

45. The Secretariat could develop a repository of technical information on the environmental impact of old, abandoned, and/or sea dumped chemical weapons in order to facilitate knowledge sharing through the Secretariat. This type of information contains useful data for understanding the environmental fate and transport of chemical warfare agents, which has value for investigative and retrospective analysis. *For further consideration, see paragraphs 237 to 240 of Annex 1.*

46. Investigative techniques required for the verification of use of toxic chemicals include approaches used by the forensic community. The Secretariat, in consultation with relevant experts, should identify such commonly used forensic techniques and protocols to assess their applicability for its own activities. *For further consideration, see paragraphs 269 to 288 of Annex 1.*

47. The SAB supports the project to upgrade the OPCW Laboratory to a Centre for Chemistry and Technology. This would enable the Laboratory to increase capabilities to meet its expanded mandate. An upgraded facility would be better able to facilitate proficiency testing and confidence building exercises, contingency operations, the handling and storage of authentic samples, provide training, and bring higher scientific visibility to the OPCW. *For further consideration, see paragraph 254 of Annex 1.*

Advice on assistance and protection

48. In order to enhance OPCW's capability to assist States Parties in response to a chemical weapon attack or incident involving toxic chemicals, the Secretariat should strengthen its preparedness and monitor advancements in medical countermeasures, detection, physical protection, and decontamination. *For further consideration, see paragraphs 294 to 319 of Annex 1.*

Advice on science and technology of relevance to chemical safety and security

49. The SAB encourages the Secretariat to engage with technical experts to ensure that its efforts to assist States Parties with chemical safety and security have a sound scientific and technological foundation. *For further consideration, see paragraph 320 of Annex 1.*

50. The SAB recommends that the Secretariat encourage research in chemical security to prevent toxic chemicals from being acquired by non-State actors with intent to use them as chemical weapons. The research support programme under Article XI provides a possible mechanism. *For further consideration, see paragraphs 325 and 328 of Annex 1.*

51. The SAB has been informed that a number of States Parties, where the economies are either developing or in transition, have expressed interest in improving their chemical safety and security capabilities, specifically with regard to monitoring the transfer of chemicals into and out of their territories. The SAB recommends that the Secretariat strengthen its partnerships with international organisations engaged in the research and development of technologies for this purpose. Further, the SAB recommends that the Secretariat pursue collaborative projects with such organisations in order to develop additional internal expertise to assist States Parties. *For further consideration, see paragraphs 327 to 329 of Annex 1.*

Advice on scientific literacy and science advice

52. Greater interaction between the SAB and Secretariat staff who perform operational roles would strengthen the Board's ability to identify science and technology-related issues facing the OPCW and augment the Board's ability to provide practical advice. *For further consideration, see paragraph 331 of Annex 1.*

53. Given the increasing degree to which scientific and technological change impacts the effective implementation of the Convention, the Secretariat should continue to strengthen its capability to monitor and forecast developments and their implications. *For further consideration, see paragraphs 332 to 333 and 339 to 351 of Annex 1.*

54. Both the Secretariat and the SAB should maintain a "watching brief" in the areas most likely to have the greatest impact on the Convention's verification regime. In particular, these include chemicals and technologies that markedly increase potential for the hostile use of chemicals, as well as technologies that provide substantially enhanced capabilities for verification purposes. In maintaining this "watching brief", the SAB and the Secretariat should be mindful of the importance of separating technological possibility from demonstrated technological capability. *For further consideration, see paragraphs 152 to 160 and 168 to 288 of Annex 1.*

55. In view of the increasingly interdisciplinary nature of advances in science and technology relevant to the Convention, the SAB should continue to build close working relationships with relevant professional societies and science advisory bodies of other relevant international organisations to enable it to identify and assess developments that may impact the Convention or the OPCW. Such relationships should also be utilised to raise awareness of the Convention and to promote its norms. *For further consideration, see paragraphs 332 to 333 and 346 to 352 of Annex 1.*

56. The SAB briefings to States Parties and the "Science for Diplomats" sessions held on the margins of meetings of the Executive Council and Conference of the States Parties have fostered greater discourse between scientists and policy makers and promoted greater scientific awareness. These initiatives should continue. *For further consideration, see paragraphs 334 to 338 of Annex 1.*

Annexes (English only):

Annex 1 Analysis of Developments in Science and Technology Relevant to the Chemical Weapons Convention.

Annex 2: List of Reports of the Scientific Advisory Board and its Temporary Working Groups, and Related Documents of the Scientific Review Process.

Annex 1

ANALYSIS OF DEVELOPMENTS IN SCIENCE AND TECHNOLOGY RELEVANT TO THE CHEMICAL WEAPONS CONVENTION

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ADVANCES IN SCIENCE AND TECHNOLOGY

The convergence of chemistry and biology

Status at the Third Review Conference

1. The SAB report to the Third Review Conference (RC-3/DG.1, dated 29 October 2012) noted that there has always been an interdependence between the sciences of chemistry and biology. What is changing is the unprecedented growth in our understanding of the fundamental processes of living systems, defined by chemical reactions and chemical structures. These advances are driven through interdisciplinary research that develops and applies increasingly sophisticated and powerful instrumentation and experimental techniques.

Implications for the Convention

2. The convergence of chemistry and biology – and implications for the Convention – were examined from November 2011 to November 2013 by the SAB's TWG on the convergence of chemistry and biology (final report published in June 2014), and in two Spiez convergence workshops held in 2014 and 2016. Participants noted a broad range of scientific disciplines are converging, including chemistry, biology, materials science, computer science, engineering, information theory, network theory, mathematics, quantum mechanics, and more. Scientific practices, across all fields, continue to evolve through transdisciplinary approaches. How far and at what speed such advances progress depend largely on developments in other disciplines acting as enabling technologies. These include data computation (and management of large databases), nanotechnology, robotics, systems automation, and many other areas.

3. Assessing the significance of such developments in chemistry and biology for the Convention, and particularly for its verification regime, needs to be informed not by what is scientifically possible, but what is likely to result in practical applications. Many reports published on this topic have approached the issue from the perspective of what is theoretically possible. Few articles have assessed what is realistically achievable, taking into account real conditions and constraints, for example, in industry. Risk and context analysis, therefore, are important from scientific discovery to fieldable application.

Production using biological and biologically-mediated processes

4. The past few years have seen significant investment in the development of biotechnologies for chemical production. Their adoption for commodity chemical production (large volumes, low cost per-unit-volume) has slowed as oil prices have dropped (making traditional chemical production processes more economically viable). Biotechnologies are increasingly being used for producing specialty chemicals (low volumes, high cost per-unit-volume), where the diversity of chemical properties and function available through harnessing metabolic processes as production tools, are highly desirable (in chemical sectors that include pharmaceuticals, flavours, and fragrances). Trends in adoption of biotechnologies across different sectors of chemical production are expected to be dynamic, with

influences that include (but are not limited to) bio-economy incentives across a number of States Parties, oil prices, initiatives to reduce reliance on oil, and the economics of feedstocks (e.g. biomass) for chemical production. The Secretariat should monitor trends in industrial chemical production and technologies being developed and deployed.

5. The SAB maintains the view that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis as used in the Verification Annex, Part IX, subparagraph A.1(b).[15] As adoption of biotechnology for chemical production moves forward, facilities will continue to come online that can produce organic chemicals in quantities that should make them declarable. The Secretariat should continue to assess the possibility of conversion of any such facilities to the production of scheduled chemicals; the outcome of such a review would inform the degree of relevance these facilities have to the object and purpose of the Convention. This assessment would also serve as a basis to consider whether there are grounds to exempt certain types of facilities or a need to review thresholds for declaration and inspection of other chemical production facilities (OCPFs). The SAB encourages furtherance of the on-going discourse on the meaning of "produced by synthesis" between the Secretariat and States Parties through consultations on chemical industry and other Article VI issues (see for example S/1534/2017, dated 14 September 2017). This will help ensure that relevant stakeholders remain adequately informed of the impact of biotechnologies on chemical production.

6. Industrial scale chemical production using fermentation processes requires selection of microbial strains capable of reproducibly producing desired chemicals at scales and sufficient quality to be economically viable. This can require significant efforts in strain engineering and selection that requires testing on various production scales. Industrial processes involve informatics, automation and significant molecular biological characterisation. For these reasons, developing reliable fermentation-based processes with genetically modified organisms may not be as simple as often described in security discussions on biotechnology. However, for malicious purposes, scaled-up and high-quality production may not be needed to obtain material in sufficient quantity to violate the prohibitions of the Convention.

7. Genomic modification capabilities (see also the section on metabolic engineering) have improved the activity, selectivity, solvent tolerance and general robustness of biocatalysts or enzymes for an increasing range of chemical reactions. In some cases, genes have been introduced into microorganisms to enable them to produce specific chemicals of interest. Synthetic biology is reducing the barrier to entry and time

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15 The SAB recommended at its Nineteenth Session and in its report to the Third Review Conference, that the term "produced by synthesis" in subparagraph 1(a) of Part IX of the Convention should cover any process designed for the formation of a chemical substance (see SAB-19/1, dated 12 September 2012; and RC-3/DG.1, dated 29 October 2012). The SAB further recommended in the report of the TWG on the convergence of chemistry and biology that the TWG on verification should consider relevant implications for verification from this recommendation (SAB/REP/1/14, dated 26 June 2014). The TWG on verification further deliberated on this question and upheld the previous SAB recommendation on this question (SAB/REP/1/15, dated June 2015).

requirement for building customised biological machines. A wide variety of enabling technologies have been used. It is conceivable to use these approaches to synthesise toxic chemicals, toxins, bioregulators, or their precursors, in quantities that could challenge the Convention. On balance, though, these technologies are bringing benefits, in medical countermeasures (MedCMs), decontamination, protective equipment, detection and biosensors as noted later in this report. Regarding synthetic biology and other methods that enable genomic modifications, there is a view that these developments deskill and reduce resource requirements compared to existing methods; this view is somewhat misleading. Certain traditional skillsets and resources required for a genetic engineering laboratory are certainly reduced. However, there is a need for different types of resources, skills and knowledge to take full advantage of the opportunities the new developments enable.

8. Although metabolic pathways are known for some phosphorus, sulfur, fluorine (PSF) chemicals, there are no known examples of the production of Schedule 1 chemical warfare agents (CWAs), such as nerve agents or blister agents, or their chemical precursors, through biological means.

9. While the technical capability to chemically synthesise many toxins exists today, there are practical limitations with regard to scale and complexity. The threat of possible misuse of this technology in relation to the Convention is therefore considered low at the present time. Synthetic biology could be used to produce toxins; in vitro production of the Schedule 1 toxins saxitoxin and ricin has been demonstrated. However, obtaining proteinaceous toxins, such as ricin, in quantity from their natural sources is much simpler than using metabolic engineering or synthetic biology. Obtaining saxitoxin from its natural sources, though inefficient, is sufficient to supply the small quantities (milligrams) required for legitimate needs, but would not be appropriate for a chemical weapons programme (which requires at least kilogram quantities). Future developments affecting the cost, efficacy and availability of relevant enabling technologies may necessitate reviewing the likelihood of using these approaches to acquire toxins.

<u>Chemical synthesis of biological agents</u>

10. A broad range of viruses can now be chemically synthesised. Chemical synthesis of simplified mycoides strains has been reported and work is underway to synthesise simplified genomes of Escherichia coli and yeast strains. The assembly of complete horsepox virus from synthesised oligonucleotides (short sequences of DNA) has also been demonstrated. The technologies that may enable the chemical synthesis of replicating organisms are becoming more accessible, but the skills required remain in relatively few facilities. In most cases, and currently, obtaining bacteria and viruses from their natural sources, or from commercial suppliers, is simpler than through employing chemical synthesis, metabolic engineering or synthetic biology approaches to make them. In regard to ability to produce highly complex genomes, a new initiative, Genome Project-write (GP-write) has been launched to synthesise a complete human genome, it is estimated that such an undertaking (3 billion bases over 23 chromosomes) will require at least 10 years. For reference, a project to synthesis a yeast genome (11 million bases total over 16 chromosomes) reported completion of

the first chromosome in 2011 and is expected to take until 2020 to complete the rest. The reported horsepox virus genome had a size of 212,000 base pairs.

11. With regard to producing synthetic genomes, a current limitation is the ability to predict whether or not the incorporation of the genome into a cell will result in a functional organism.

Enzymes

12. Every cell, from the simplest to the most complex, relies on chemical reactions accelerated by enzymes. Enzymes are proteins that are more complex in structure than any man-made catalyst available today. Despite their ubiquity and versatility and a general understanding of their functionality, the molecular mechanisms that underpin enzyme reactivity are far from being entirely deciphered in most cases.

Directed evolution of enzymes for synthesis and production of chemicals

13. Advanced computational methods and directed evolution are used to develop enzymes tailored to address specific needs. Given recent advances, it is now possible to tailor enzyme properties to drive chemical reactions with high selectivity and yield.

14. Directed evolution can be applied to naturally-occurring enzymes with the desired functionality or artificial enzymes that, based on theoretical models, are predicted to have the desired reactivity and selectivity. Regardless of the starting point, the genetic sequence that describes the enzyme can be inserted into a bacterium, such as E. coli, which is then cultured in a well-plate, to allow naturally-occurring mutagenesis to vary that genetic structure. This generates a large number of candidate sequences (~2 weeks for 2000 variations) which can be separated and screened for activity.

15. The variations can be assayed and ranked in efficiency using microfluidic screening systems. Some variations will demonstrate improved function for the desired purpose compared to the native enzyme, and some will not. Those demonstrating the most promise can be used in another round of directed evolution to optimise the molecule.

16. Industrially, enzymes with improved activity and stability can be used to increase the efficiency of production processes, reducing wastes and increasing yields. For example, the directed-evolution-designed paraoxonase, an organophosphorus (OP) hydrolase enzyme, can hydrolyse the OP pesticide paraoxon, and OP nerve agents, many times more efficiently than the native enzyme.

Enzymes as decontaminants

17. Considerable effort over several decades has been invested in the development, mainly from microorganisms, of efficient organophosphorus-degrading biocatalysts, among them organophosphate hydrolases. These enzymes have been considered for biobased decontamination of chemicals, and strategies, such as immobilisation on a variety of supports, have been studied, to increase stability, activity and the development of green decontaminants. Other enzymes that have the capability to hydrolyse organophosphorus compounds include diisopropyl fluorophosphate fluorohydrolase, laccases (copper-containing oxidase enzymes), organophosphate acid

anhydrolase (OPAA) and related prolidases, paraoxonase, phosphotriesterase-like lactonase and SsoPox (a highly stable enzyme isolated from the marine bacterium *Sulfolobus solfataricus*, a resident of hydrothermal vents).

18. Haloalkane dehalogenases have been employed for decontamination of sulfur mustard, where the hydrolysis proceeds via non-toxic intermediates. The major limiting factor to fieldability is the poor water solubility of sulfur mustard. If sulfur mustard is added to an organic solvent miscible with water, the agent and enzyme readily dissolves, and rapid hydrolysis of the blister agent can occur. However, the unsatisfactory stability of the dehalogenase enzymes in organic solvents can limit such applications. Novel dehalogenases, and/or immobilised/engineered enzymes combined with nanotechnologies, with improved stability, could overcome these limitations.

19. There are also enzymes that appear promising for neutralising hydrogen cyanide, cyanogen chloride and arsine. Cyanide can be enzymatically converted to the less toxic thiocyanate by rhodanases (thiosulfate-cyanide sulfurtransferases, thiosulfate sulfurtransferases, thiosulfate thiotransferases).

20. Enzymes are appealing because they offer a non-corrosive, safe and catalytic means to decontaminate CWAs. Like many processes that employ enzymes, biodegradation of CWAs has limitations; overcoming this requires improved stability and detoxification efficiency of the enzymes. Immobilisation has been proposed to reduce enzyme biodegradation, and protein engineering has been used to increase catalytic efficiencies of recombinant enzymes. Computational enzymology, using molecular modelling, has improved knowledge of the mechanisms of action of enzymes, and has contributed to advances in the engineering of more efficient enzymes. The discovery of highly thermostable organophosphorus compound-degrading enzymes such as SsoPox, and their engineering for higher activity, might enable the development of economically-viable organophosphorus bio-decontaminants.

Enzymes in biosensors

21. Recent developments in detectors and monitors that include a biological sensing element, such as an enzyme or antibody, have included miniaturised disposable biosensors, particularly as point-of-care diagnostic devices. These diagnostic tools could be useful for on-site inspection-related activities. Most biosensors for the detection of organophosphorus nerve agents, or pesticides with similar acetylcholinesterase (AChE) inhibitory activity, measure AChE or butyrylcholinesterase (BuChE) inhibition, or organophosphorus compound hydrolysis by enzymes (e.g. phosphotriesterase). An antibody-based biosensor for sulfur mustard is commercially available. Biological sensing has long been a major component of detection systems for biological toxins, including saxitoxin and ricin.

22. Many published reports describe efforts to engineer enzymes, antibodies and other biological receptors as sensing elements for the detection of chemicals.

23. An innovative approach is the use of sensor proteins involved naturally in olfaction, especially those of insects. Such biosensors may enable real-time detection of a variety of chemicals. Behavioural changes in insects after exposure to chemicals

(including sarin and sulfur mustard) have been suggested as a means of providing early warning to humans of the presence in the environment of a toxic chemical. These approaches remain research projects at this time.

Metabolic engineering

24. Metabolic engineering is the use of genetic engineering to modify the metabolism of an organism: this can involve the optimisation of existing biochemical pathways or the introduction of new pathways. Bacteria, yeast or plants, are most commonly engineered for production of specific metabolites for medicine or biotechnology. Metabolic engineering seeks to model the chemical networks employing biochemical reactions and enzymes to allow cells to convert raw materials into molecules necessary for the survival of cells, and identify parts of the network that constrain their production. In the case of degradation or complete mineralisation of a toxic material, engineered organisms can have applications for bioremediation.

25. The ability to manipulate genomes and function in biological systems is an enabler for tailoring biological (metabolic) processes to produce chemicals. The SAB notes that many different terms are used for the tools and methods available; these include metabolic engineering, synthetic biology, gene editing, directed evolution and more. Advances under of any of these terms can contribute to advancing biomediated chemical production capabilities. In the next section of this report, metabolic engineering is described, but it should be appreciated that the outcomes of this field can also be realised using science categorised under different terminology.

Advancements in metabolic engineering

26. Although it can be said that metabolic engineering started centuries ago with the production of fermented products, such as wine, bread and cheese, the general and modern application involves the alteration of genome sequences, or introduction of plasmids into microorganisms, by techniques of modern molecular biology. Therefore, the emergence of uncontrolled or controlled mutation techniques, DNA shuffling and CRISPR[16] genome editing, among other continuously advancing technologies has impacted and accelerated the production of bio-products from engineered metabolic pathways.

27. Metabolic engineering has value for many of the applications where biocatalysis has been pursued: for example, the synthesis of complex natural products, or preparation of homochiral compounds. In addition, it can be useful even when alternative traditional chemical synthetic approaches are available if the chemical route is precluded by regulations, patents or environmental considerations.

28. Modern techniques have provided the potential to have biocatalytic alternatives for a broad range of organic reactions. These reactions could potentially be engineered into

16 CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats. The term refers to short segments of DNA sequence that are fundamental components of the bacterial defence system on which CRISPR-Cas9 genome editing technologies ae based.

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the metabolic pathways of an organism, provided the substrate and product are not toxic to the organism, or can be rapidly metabolised into less toxic compounds. The toxicity referred to here is to the engineered cell, not to animals and/or humans.

Potential impact on the Convention

29. For applications involving degradation of chemicals, microorganisms or plants can be designed or modified to resist or metabolise CWAs and/or other toxic chemicals. Modified *Pseudomonas putida* bacterial strains can use the insecticide parathion as a source of carbon and energy. However, the capacity of a microorganism to degrade, or utilise, a given chemical as its sole source of carbon does not imply that the microorganism will prefer to utilise this metabolic route if other sources of energy are available. Results of experiments performed inside a reactor under carefully controlled conditions should not be directly extrapolated to potential use in the field use, as appropriate testing would be required before such a possibility could be realised.

30. As catalysts can potentially catalyse chemical reactions in both forward and reverse directions, the development of microorganisms capable of hydrolysing and therefore inactivating organophosphates, opens the possibility of also catalysing the reverse reaction (e.g. their formation). Enzymes that can form or cleave carbon-chlorine bonds, or form carbon-arsenic bonds, are known. This raises the possibility of the development of biological or at least enzymatic routes for destroying or producing CWAs. Facilities involved might not resemble traditional chemical facilities dedicated to the synthesis of Scheduled chemicals (although containment and safety precautions for such chemicals would have recognisable similarities to those found in traditional facilities). An enzyme, like any catalyst, does not influence chemical equilibrium; thus, reversing an OP hydrolysis reaction might be a challenge, particularly in aqueous media. Such considerations might decrease the likelihood of the development of practical biosynthetic routes to traditional CWAs.

31. It is possible to genetically modify toxin-producing plants to increase the production of a toxin, or extract the genes that encode for that particular synthesis and express them in a microorganism as an alternate means of producing the toxin. The limits for that approach are not technical but, currently, the complexity and required expertise make them impractical (and potentially resource and tacit knowledge-intensive) as compared to traditional extraction methods. For example, to engineer a yeast strain to produce opioids, genes from several poppy plants, a bacterium and a mouse had to be added to the yeast strain; of significance here was that the genetic pathway from the opium poppy alone was not what ultimately provided the modified organism capability.

32. Likewise, conditions where modified organisms produce chemicals might require further optimisation; in the case of the opioid producing yeast, the researchers showed that no opioids were produced from the yeast under fermentation conditions used for brewing beer.

33. Metabolic engineering has potential for transforming the chemical industry and for producing microorganisms with decontamination and bioremediation applications.

Such advances might permit in future the manufacture of toxic compounds that could potentially be weaponised. The skills required by inspectors for recognising production facilities utilising metabolically engineered microorganisms might be reviewed. Bioproduction facilities differ from those involved in traditional chemical manufacture in equipment, size, potential for numbering-up (as an alternative to scale-up), and training of personnel. The SAB notes that certain aspects of a traditional chemical plant that produces highly toxic chemicals, for example containment and safety measures, would have to be replicated in traditional and biomediated production facilities, and hence be familiar to inspectors.

Nanotechnology

<u>Status at the Third Review Conference</u>

34. The SAB's report (RC-3/DG.1) briefly described nanotechnology, which was identified as a rapidly expanding area of scientific advancement with contributions to materials science, medicine, electronics and energetics. Carbon nanotubes, the use of nanoparticles in medicine for smart drug delivery, and the contribution of nanotechnology in improved diagnostics were identified.

35. The potential of nanomaterials to enhance acute (short term) or chronic (long term) toxicity of chemicals and materials normally regarded as inert was considered a risk. It was recognised that beneficial applications for chemical security were being developed which included: diagnostic point-of-care devices for nerve agent, biological agent and toxin exposure. The development of new detectors is possible using electronic and optical properties of nanomaterials. Novel decontaminants utilising the increased reactivity and high absorptive capacity of nanoparticles, inclusion of nanofibres into lightweight protective clothing, and more effective respirator filter materials, have been demonstrated.

36. It was recognised that nanotechnology has the potential for applications for purposes prohibited by the Convention with concerns that the delivery of therapeutic drugs could be exploited for the delivery of toxic chemicals and that nanoparticles may have enhanced acute toxicity compared to larger particles. The risk to the Convention from nanotechnology was regarded as low; however, it was recognised that there was a danger that nanotechnology could be exploited for the development of new toxic chemicals.

<u>Nanotechnology and convergence</u>

37. Nanotechnology facilitates further convergence between chemistry and other scientific disciplines such as biology and physics, which may have implications for the Convention. Advances in nanotechnology particularly those that could be used to improve defensive countermeasures to CWAs should be monitored.

38. As with other advances in drug delivery, nanotechnology may have potential for application to purposes prohibited by the Convention. For example, the enhanced delivery of therapeutic drugs to their biochemical target could be exploited to deliver toxic chemicals to humans. However, there are significant differences between the administration of a nanomedicine and the deployment of a chemical weapon. The

practicality and risk of this approach to develop a chemical weapon is currently considered to be low.

39. It is possible to generate nanoparticles with arrangements of hydrophilic and hydrophobic compounds on a length scale similar to biological materials, so called "patchy particles". This allows the development of systems that are entirely synthetic in nature but mimic certain biological functions, and this may open new opportunities in medical treatment, decontamination and other fields. Nanotechnologies for delivery of DNA as well as tools for editing DNA in cells have been demonstrated.

40. Nanostructures built from single stranded DNA (often referred to as "DNA origami") are at a fundamental research stage with few currently recognised applications. The goal of this research is to create molecular tools that interact in a type of "nanofactory" or to develop molecular robots. DNA origami may be integrated with DNA computing or possibly used for drug delivery using nanocontainers with external release triggers.

41. On whether or not nanotechnologies as weapons are covered by the Convention, the SAB notes that nanotechnologies that impact life processes through chemical action and if used for purposes prohibited by the Convention are covered under the Article II "general purpose criterion": they would constitute chemical weapons. Likewise, nanotechnologies used to deliver chemical or biological agents would make nanoparticles a type of delivery system, which would prohibit them under the Convention and under the Biological Weapons Convention.

42. As advances in nanotechnology play an important role in improving drug delivery, protective equipment and biosensors – and given that nanotechnology may have potential application to purposes not prohibited by the Convention – advances in nanotechnology should continue to be monitored and periodically reviewed.

43. An overview of recent publications on applications of nanotechnology for chemical analysis, detection, protection, decontamination and MedCMs against CWAs, showed that few commercially available products are currently available.

<u>Protective equipment and decontamination and recommendations</u>

44. Nanotechnology in the development of physical protective equipment has been primarily directed at enhancing protection whilst reducing the physiological burden and physical restrictions of respirators and clothing. Approaches taken include the incorporation of enzymes or catalysts to develop self-decontaminating protective clothing and the use of nanomaterials with improved properties in canister filters and clothing. The use of enzymes is appealing as they offer a non-corrosive, safe and catalytic way of decontaminating CWAs. Like other processes and fieldable technologies that employ enzymes, biodegradation of CWAs presently has limitations. Research to overcome these limitations includes the use of nanotechnologies to improve enzymatic formulations to enable higher enzyme activity and stability (including in non-aqueous environments). Advances in research in this area have also benefited from developments in the convergence of chemistry and biology.

45. The OPCW should monitor advances in protective equipment with possible applications for inspectors. Trade shows in CBRN protective equipment should be attended by the Technical Secretariat annually, and opportunities to evaluate and field test new equipment be considered. This could potentially be enabled through incorporating a "field testing" function within the Inspectorate.

Detection and biosensors

46. Nanotechnology has enabled advances in detection technologies, including biosensors incorporating biological sensing elements such as enzymes or antibodies, particularly point-of-care diagnostic devices. These devices could be useful for on-site inspections.

47. Solid or thin-film nanocatalysts, prepared from graphene oxide and carbon nanotubes functionalised with multiple catalytic groups, in combination with metallic nanoparticles, for the degradation of OP pesticides, have demonstrated their potential as pesticide (and possibly nerve agent) sensors. They could be used in conjunction with Surface Enhanced Raman Spectroscopy (SERS) detection as well as visible spectroscopy if coloured degradation products can be produced.

48. Paper-based electrochemical devices fabricated with carbon-based nanostructures or printed carbon black have been constructed into flexible, foldable, and wearable biosensors, using, for example, nicotinamide adenine dinucleotide as a sensing element. This research might lead to low cost, low weight and flexible sensing devices.

49. At the present stage of development, on-site biological detection in real-time, while challenging, has been demonstrated with nanopore-based sequencing tools that can collect sequence data and compare them to a reference genome as the sequencing is underway, allowing on-site identification of pathogens. The nanopore based technologies have been used in West Africa for Ebola detection and to track infection outbreaks in hospitals.

Medical countermeasures (MedCMs)

50. Encapsulation of catalytic bioscavengers (including enzymes such as BuChE) inside nanoparticles can improve stability for storage, as well as in blood, in the latter case nanoparticle supports help reduce the immune response. However, the availability of bioscavengers as MedCMs has been in discussion for many years, the SAB does not anticipate availability in the near future. Delivery of such countermeasures with nanotechnologies would be expected to lag behind any eventual clinical validation of bioscavengers of current interest.

51. While nanomedicine technologies might improve MedCMs, for long-lasting action against a large spectrum of OP agents, in terms of efficacy, safety and cost, the field is in its infancy. Additionally, the market size for nanotechnology MedCMs for CWAs is too small to drive rapid development and clinical validation. Currently, only a limited number of animal studies have been published on potential nanomedicine-based nerve agent countermeasures.

52. The SAB noted the importance of clinical data when considering the potential of new medicines, as it is estimated that as much as 50% of pre-clinical life science research does not, for various reasons, translate into clinical applications.

Green and sustainable chemistry

53. As expressed by the Director-General in his opening remarks to a Green Chemistry Expert Group Meeting held at OPCW in 2016, "the promotion of peaceful uses of chemistry and a culture of safety and security among chemistry professionals is at the heart of the OPCW mandate". Safe and secure handling of chemicals is also a key focus in the chemical industry where it is recognised that safety and security play a vital role in chemical management.

54. Green chemistry seeks to develop chemicals and chemical processes that do not harm health and the environment. The field is often defined as the design of chemical products and processes that reduce or eliminate use and generation of hazardous substances. Reducing chemical hazards would include precursors, products, intermediates, and/or by-products of chemical processes. Green engineering is a term applied to the design and implementation of green chemistry.

55. A set of 12 principles have been developed to guide green chemistry research, a set of 12 principles also exist for green engineering. Embodied within these principles is an objective to adopt more efficient processes that do not generate harmful chemical waste. The use of safer chemicals and processes, design of safer chemicals, use of degradability as a key property of materials to avoid toxic waste, and the design of inherently safer chemistry to reduce risk and impact of a chemical incident, are inherent to these principles, which align with the objectives of The Hague Ethical Guidelines and the norms of the Convention.

56. The SAB recognises that one may never find a truly non-toxic chemical (all chemicals have a toxic dose), but notes that scientific developments seeking to reduce risk and produce safer processes and less toxic chemicals are important for scientists to pursue.

Green and sustainable chemistry in industry

57. Whether green chemistry can provide safer industrial processes and chemicals that pose less risk than those employed in industry is not a given; each case would need to assess the risk reduction and consider the full product life cycle. If toxic chemicals are handled with the necessary safety measures in place, they may not present higher risks than processes involving less-toxic chemicals (especially important for these considerations are the by-products and waste-products).

58. In the chemical industry, "sustainable chemistry" has played a role in the development of chemical products. Recent and ongoing efforts seek to improve safety and security in the handling of such products. Adoption in industry has been achieved through maximising hazard awareness at every level of the supply chain. In this way, exposure to toxic materials is reduced through the increasing use of sophisticated production and transport equipment and by training of personnel. An essential component is the performance of chemical and toxicological risk assessments (which is embodied within the principles of green chemistry).

59. Sustainable chemistry can include broader considerations than green chemistry, with a focus on innovation to enable more sustainable social, environmental and economic outcomes. The development of less hazardous chemicals is a key element of green and sustainable chemistry discourse; with sustainability discussions also focusing on reducing hazards and risk, including (but not limited to) reduced resource footprints, enhanced energy efficiency, emission reductions, and clean water. Chemical safety and security have been recognised as prerequisites for sustainable chemistry.[17]

Conclusions and recommendations

60. The SAB notes that Article VII, paragraph 3 of the Convention, in reference to national implementation states that, "[e]ach State Party, during the implementation of its obligations under this Convention, shall assign the highest priority to ensuring the safety of people and to protecting the environment, and shall cooperate as appropriate with other States Parties in this regard." Furthermore, the Hague Ethical Guidelines include as the core element, "Achievements in the field of chemistry should be used to benefit humankind and to protect the environment." In this regard, the SAB recognises that research and developments from green and/or sustainable chemistry communities and initiatives provide opportunities to promote the norms of the Convention and can contribute to reducing safety and security risks associated with chemicals and chemical production. Green and/or sustainable chemistry can serve to enable greater collaboration between industry, governments and international organisations.

61. The SAB notes that scientific research (including green chemistry) that promotes the norms of the Convention and contributes to peaceful uses of chemistry should be encouraged, including by giving consideration of support to relevant projects and initiatives through Article XI programmes, and in promoting a safety and security culture in scientific pursuits. The SAB realises that not all scientific discoveries are practical to implement into industrial processes or are economically viable; this does not contradict supporting and/or encouraging green chemistry research, but serves to remind that real-world (fieldable) capabilities and suitability for applications of interest, rather than "scientific fashions", should be considered paramount when assessing the suitability of any new scientific discovery or technology for specific applications relevant to the OPCW or the implementation of the Convention.

62. Realisation of green and sustainable chemistry objectives would help reduce access to toxic chemicals, which has benefits for chemical safety and security. As the Secretariat furthers its work in chemical security, there may be opportunities to leverage research ideas from green and sustainable chemistry researchers into innovative chemical security applications.

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17 This was identified during an ICCA-UNEP Workshop on the Role of Chemistry in Achieving Sustainable Development held from 11-13 September 2016 in in Shanghai, China. See https://www.icca-chem.org/wp-content/uploads/2017/01/Key-Takeaways_ICCA-UNEP-Workshop_Shanghai_final.pdf

Computational chemistry

63. Computational methods that use theoretical models and/or previously collected datasets to study and predict chemical properties can be useful for providing insight on stability, reactivity, decomposition, and decontamination of toxic chemicals. The information produced might still require experimental validation, but the results can better inform how to proceed and reduce the number of actual tests with the toxic materials required to generate data. As the models and methods available become more advanced, computational tools will become more useful in support of field and laboratory work.

64. Computational studies on CWAs have included adsorption and hydration studies to inform sensor development and degradation on catalytic metal oxide and self-decontaminating surfaces, microhydration studies to understand hydrolysis mechanisms and spectral detection in humid air, and supramolecular complex formation relevant to the design of catalytic nerve agent scavengers. Computation studies of enzymatic degradation of OP compounds have provided promising predictions for the remediation of CWA contamination.

65. Computational tools have been applied to the screening of new drug candidates, and for the identification of gene and protein expression patterns in vitro and in animal models, to support toxicology and medical studies. These tools can provide insights into potential therapeutics for CWA exposure. The application of computational tools in toxicology and their relevance to MedCMs are also discussed in other sections of this report.

Big Data, informatics and artificial intelligence

66. Information and communication technologies play a key role across twenty-first century scientific development, and the integration of these technologies with (bio)chemical, spatial, temporal and other data streams has potential application for chemical security including recognising unexpected or unusual (bio)chemical change in the environment in real time. Change from exposure to chemical agents might be sensed using remote monitoring and automated systems. Such integrated technologies might enhance capabilities in both early warning and investigation. Examples are sensor development, precision agriculture, mobile and wearable technologies, digital health, autonomous sample collection and analysis, satellite image analysis, and technologies that enable real-time analysis and decision-making. These have potential application for supporting chemical disarmament and the Convention.

67. The SAB notes that technologies that integrate informatics, mobile devices and remote sensing (including automated systems and satellite technologies) with an expanding range of capabilities are becoming increasingly accessible. The Convention's science review process should continue to keep abreast of developments in these areas, and the Secretariat might consider where such tools might benefit OPCW and look for opportunities to field test them.

Big Data

68. Advances in computational hardware and software have made large-scale analysis more accessible, increasing the quantity of data that can be processed with personal computers and mobile devices. Large datasets are collected and analysed to reveal insights into business, safety, politics, society and the environment. Such analytics can be used to potentially recognise emerging opportunities and threats. Big data has been used to track and manage energy consumption, monitor supply chains (which could include chemical supply chains and life cycles), analyse the output of sensor networks, guide business decisions, and for combating crime and acts of terror. While much is possible, ensuring the data contain the necessary inputs and are of sufficient quality to provide verifiable outputs from analysis is critical and can pose challenges. Cyber security, and how to validate information used as input for analysis and legal aspects of the use of Big Data, are also concerns.

Artificial Intelligence (AI)

69. Artificial intelligence (AI) tools are becoming more accessible, and can provide capabilities for automating workflows and helping recognise unusual features in information through data mining (Big Data analysis), especially for threat assessment for counter terrorism.

70. AI has been used in chemistry since the 1950's, and its potential for advancing scientific development and capabilities has advanced greatly in recent years, with incorporation of deep convolutional neural network architecture into classical AI architecture. Uses include exploring scientific literature, predicting chemical properties, suitability for specific applications, absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction, chemical discovery, and designing chemical synthesis routes.

71. When databases are available, AI tools can be used to mine and integrate data effectively, returning information that can link a given result to further information of relevance. This can be of value in matching sampling and analysis results to reference materials (for example identification of a given chemical and also matching a given sample to other samples of the same chemical in a database).

72. Another area where AI is finding application is in object/image recognition, where a digital image taken by a mobile device can be analysed, its content recognised and matched with potentially valuable and actionable information through a mobile app. This has been used in agriculture, where an image of a plant organ (e.g. a leaf) can be used to diagnose a crop disease based on observable phenotypic characteristics, and identifying pills and other pharmaceutical products. The ability to produce air quality information (e.g. particulate counts) has also been demonstrated using images of specific landmarks in a city. These methods require training data and validation, with analysis capabilities certain to continue improving as AI research progresses. A Convention-relevant application could be identifying munitions or recognising laboratory equipment (and providing relevant information) from on-site photographs.

Recommendations

73. The development of reliable AI tools is non-trivial. Hurdles to their adoption include access to adequate training datasets and their validation. Development of such tools benefits from working with external partners. There is also a dual-use potential from the use of AI analysis and design to enable access to procedures for production of toxic chemicals. Developments in chemical applications of AI (including those having dual-use potential) should continue to be monitored by the Secretariat.

74. AI has received a lot of attention for its potential enabling capabilities and potential security risks. AI software companies are making algorithms available for developers and digitalisation. These tools will continue to be adopted and improved upon. Advances in computational methods for enabling chemistry are expected to continue and a watching brief should be maintained. The enabling power of information analysis through AI is further described in the verification relevant technologies section of this report.

75. The SAB recommends that the Secretariat ensures that expertise in informatics and the use of AI tools be given due consideration when evaluating the capabilities required for the Secretariat to remain fit for purpose.

ADVICE ON CHEMICALS

Scheduled Chemicals

76. Knowledge of Schedule 1 chemicals, in particular their analysis, synthesis and safe handling, will need to be maintained with adequate capability to prevent the re-emergence of chemical weapons. The SAB views initiatives like the Schedule 1 Users Forum held in 2014 (Madrid) and 2018 (Spiez) as an important venue for practitioners to share specialised knowledge and experience. The SAB encourages the OPCW to continue to support this initiative.

77. Reviewing developments since the Third Review Conference, the SAB welcomed the implementation in 2015 of a procedure for handling Schedule 1 chemicals as unavoidable by-products during Article VI inspections (S/1272/2015, dated 1 May 2015).

78. The SAB notes its advice to the Third Review Conference in relation to captive use of Schedule 1 chemicals and salts of scheduled chemicals remains relevant to the Fourth Review Conference (see paragraphs 62 to 66 and 70 to 73 of RC-3/DG.1). The Secretariat and States Parties may wish to review that advice.

79. As declarations of captive use under the Convention are required to provide assurance that scheduled chemicals cannot be diverted for prohibited purposes, efforts should continue to be made to ensure that the chemical industry (via the National Authorities) in each State Party is informed on the issues related to captive use of scheduled chemicals.

80. In regard to salts of Scheduled chemicals, the SAB remains of the view that, on scientific grounds, there should be no differentiation between the treatment of the free

base and the corresponding salt. This is a reaffirmation of a recommendation first made by the Board in 1998 and noted again in the Report to the Third Review Conference.

Isotopic labels and stereoisomers of scheduled compounds

81. Isotopically labelled scheduled chemicals and stereoisomers of scheduled compounds were considered by the SAB response to a request from the Director-General (SAB-23/WP.1, dated 28 April 2016).

82. The Annex on Chemicals to the Convention comprises three schedules listing toxic chemicals and their precursors. They consist of generic descriptions of classes of chemicals, or chemical names accompanied by their Chemical Abstract Services (CAS) registry numbers.

83. Some isotopically labelled compounds and stereoisomers of scheduled chemicals have presented ambiguity as to whether they should be treated either as scheduled chemicals or as chemicals under the same schedule as their parent molecular structure.

84. Isotopic labelling (substitution) is a commonly employed technique in the study of chemicals. In relation to the Convention, isotopic labelling is used to develop analytical methods and to investigate the mechanisms of action of scheduled chemicals in natural processes. Isotope substitution is regarded as the smallest structural change in a molecule. Thus, isotopically labelled CWAs are presumably as hazardous as their unlabelled counterparts listed in the Schedules.

85. As discussed in the SAB's advice on scheduled chemicals (SAB-23/WP.1), samples of the chemicals in the Schedules would exist as mixtures of molecules containing naturally-occurring isotope ratios. As any given isotopically labelled molecule would exist in the sample at levels consistent with natural abundance, and this would not alter the status of the chemical sample on a Schedule, there is no reason an isotopically enriched sample of a Scheduled chemical should be treated differently.

86. Stereoisomers are molecules that have the same molecular formula and sequence of bonded atoms (constitution) but differ in the orientation of their atoms in space. The use of stereoisomers allows a better comprehension of the mechanisms of toxicity of chemical agents (understanding the actions of molecules on life processes). They can be classified further, for example, into enantiomers or diastereoisomers. Enantiomers have the same physical properties, except for the direction they rotate a plane of polarised light; their interaction with different optical isomers of other compounds is governed by their chirality. As a result, different enantiomers may display different biological effects (a result of biological molecules also existing in specific enantiomeric forms). Diastereoisomers are stereoisomers that are not enantiomeric and are thus not related as mirror images. Diastereoisomers show differences in physical properties and can also show differences in chemical behaviour towards both achiral and chiral reagents. As with enantiomers, the biological effects of diastereoisomers can differ.

87. Despite the fact that the potency of stereoisomers can differ, all of them can be used to affect life processes, and methods of production can potentially produce either one specific stereoisomer or a mixture of them. Given this, the SAB is of the view that the Convention should treat them equally.

88. The synthesis of pure isotopically labelled molecules and stereoisomers requires a high degree of skill and more expense than classical approaches to unlabelled or stereoisomeric mixtures of chemicals. They are used mainly on a small scale in research laboratories to help develop protective measures, in particular MedCMs.

Recommendations

89. The SAB recommends that isotopically labelled or stereoisomeric variants of scheduled chemicals should be interpreted as belonging to the Schedule that includes the parent structure. And that the structure of a chemical, regardless of its isotope pattern or spatial orientation of atoms, should determine whether that chemical falls within the Convention schedules.

90. If a chemical is included within a Schedule, then all possible isotopically-labelled forms and stereoisomers of that chemical should be included, irrespective of whether or not they have been assigned a CAS number or have CAS numbers different to those shown in the Annex on Chemicals to the Convention. The isotopically labelled compound or stereoisomer related to the parent chemical specified in the schedule should be interpreted as belonging to the same schedule.

91. Appropriate analytical data for isotopically labelled relatives and stereoisomers of scheduled compounds should be included in the OCAD.

92. Furthermore, the SAB advises that it is inappropriate to rely solely upon CAS numbers to identify chemicals covered by the Schedules. Although relevant as aids to declaration and verification, a given chemical may have more than one unique CAS number assigned to it. A CAS number should not be used as the unique means to determine whether a chemical is included in, or excluded from, a Schedule; this advice is consistent with previous SAB advice (see paragraph 3.5 of the Annex to RG-2/DG.1, dated 28 February 2008).

Riot control agents (RCAs)

93. Riot control agents (RCAs) are chemical compounds that include 2-chloroacetophenone (CN), 2-chlorobenzylidene malononitrile (CS) and oleoresin capsicum (OC), which under appropriate conditions, such as open spaces, in low to moderate concentrations, usually cause temporary disablement of individuals due to intense irritation of the mucous membranes, respiratory tract and skin. Such temporary effects make such chemicals of interest for law enforcement purposes. However, these types of chemicals can produce acute site-specific toxicity where sensory irritation occurs, as well as severe irritation of the upper respiratory tract, lungs and even death if used in confined spaces in high concentrations.

94. The Convention prohibits the use of toxic chemicals as means of warfare or intentional damage (such chemicals being defined by their chemical action on life

processes to humans and animals, and its Article II (7) defines RCAs as any chemical not listed in a schedule in the Annex on Chemicals, which can rapidly produce in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure). Toxic chemicals include CWAs and their precursors which are listed on the Schedules in the Convention's Annex on Chemicals. RCAs are permitted for use in law enforcement including domestic riot control purposes, but not as a method of warfare. In accordance with subparagraph 1(e) of Article III, the States Parties are also required to declare RCAs.

95. The SAB was requested by the Director-General at its Twentieth Session, to provide technical advice on an initial list of RCAs that had been declared by States Parties, researched, or were commercially available. The SAB advised in May 2014 that 17 chemicals from a list of 59 they had considered corresponded to an RCA as defined by Article II(7). The list of 17 RCAs (S/1177/2014, dated 1 May 2014) was provided to States Parties as a point of reference in support of their declarations.

96. Subsequently the Director-General requested the SAB to re-examine the issue, taking into account all available scientific literature up to March 2017. As a result of the new review, the list of 17 RCAs remained unchanged, but 43 additional chemicals considered by the SAB at its Twenty-Fifth Session were provided as a reference list of substances that do not meet the criteria of an RCA (and should not be declared as such) but may have historically been either used for, or considered for use as an RCA (SAB-25/WP.1, dated 27 March 2017). The SAB encourages the Secretariat and States Parties to consider this list when they review policies relating to RCAs.

Incapacitating or central nervous system (CNS)-acting chemicals

97. As previously noted, RCAs are expected to produce an immediate disabling effect on personnel. They act primarily on the sensory nerves of the peripheral nervous system in the eyes, nose, respiratory tract, and skin, having limited or no effect on the central nervous system (CNS). However, other types of disabling chemicals, historically referred to as incapacitating chemical agents (ICAs) differ from RCAs as they act primarily on the CNS. ICAs also differ from RCAs in that their effects are not usually confined to sensory irritation of a temporary nature. These compounds can induce incapacitation including cognitive impairment, loss of motor function and ultimately unconsciousness.

98. The SAB has, since its Fifteenth Session in April 2010, considered the history of the development of incapacitating chemicals since the 1950s, including the fact that no chemical has been discovered or developed that satisfies the requirements of being able to produce almost instantaneous incapacitating effects which will last for some hours with no health risks to the exposed individuals. The SAB recognised that chemicals that selectively modify CNS functions, such as the opioid fentanyl and its analogues, which are considered to be safe when used under controlled medical conditions, can have a very low safety margin when delivered as an aerosol, based on factors including uneven dissemination, variability in human response, and a need for rapid onset of action. Other examples might include other CNS depressants as well as stimulants. The SAB noted that some fentanyl analogues have lethality comparable to

the OP nerve agent VX. In view of these factors, the SAB has most recently discussed them as "central nervous system acting chemicals" rather than as "incapacitants".

Recommendations

99. Because of the dramatic increase in opioid abuse as a public health problem, research is underway to develop vaccines against synthetic opioids, such as heroin and fentanyl. Early results in animal tests on synthetic opioid vaccines are encouraging, but years of further research and testing will be needed to determine whether or not an effective immunotherapy for heroin, fentanyls and other opioids will be feasible. Currently a common countermeasure against opioid overdose is naloxone (sold under the trade name Narcan®), an alkaloid drug with a similar structure to morphine.

100. The SAB refers to its advice from the report to the Third Review Conference (see paragraphs 12 to 13 and 83 to 86 of RC-3/DG. 1), and maintains the view that the technical discussion on the potential use of toxic chemicals for law enforcement purposes has been exhaustive; the term 'non-lethal' is inappropriate when referring to chemicals intended for use as incapacitants, because for all chemicals toxicity is a matter of dosage; and that the Secretariat should commence preparations for verification activities that could be required during an investigation of alleged use (IAU), including sample collection and the use of analytical data.

101. The SAB is of the view that technical discussions on CNS-acting chemicals remain exhausted; this issue is important to the Convention and is now in the policy domain. The SAB sees no value in revisiting this topic as the scientific facts remain unchanged since the SAB first considered the issue, in the SAB's Report to the Third Review Conference (see paragraph 12 of RC-3/DG.1). The SAB recognises that CNS-acting acting compounds are not RCAs as they do not meet criteria specified in Article II paragraph 7. Furthermore, the SAB notes that there have been examples of the use of CNS-acting chemicals in law enforcement that have resulted in permanent harm and death due to an irreversible action on life processes.

Unscheduled toxic industrial chemicals (TICs)

102. Toxic industrial chemicals (TICs) pose potential hazards if released in sufficient quantities (whether intentionally as weapons or through accidental release). The potential for harm from a TIC will depend on the chemical and its volatility, toxicity, flammability, corrosiveness and reactivity. TICs may represent inhalation, oral or topical hazards, and the impact of their effects on life processes will depend on dose and exposure time.

Recommendations

103. TICs can be categorised by toxicity ranking, their principal hazard, physical state, yearly production at one or more sites, quantities globally imported and exported, and risk of exposure. Such surveys and categorisation of TICs are performed; however, they are usually not openly available. TICs are typically divided into classes of chemicals according to their risk: extremely high, high, medium, and low. As a general assumption, ~5% of TICs would probably be of extremely high concern, ~30% of high concern, ~30% of medium concern and ~30% of low concern. The

SAB recommends the Secretariat review existing surveys and categorisation of TICs to inform development of useful analytical methods. Available lists of chemicals of concern may prove helpful for these purposes.[18]

104. Research into, and a review of, products that form between TICs (e.g. chlorine) and materials that may be present during an attack, could aid sampling and analysis strategies. The materials could include metals present in common household goods, mobile phones and electronic devices, and common types of wood and plastics, for example.

Toxins

105. A toxin is a poison produced by living cells or organisms. Toxins vary greatly in toxicity, with effects that range from minor (such as a bee sting) to deadly (such as botulinum toxin intoxication) when a sufficient dosage is received. Toxins affect only those directly exposed to them. They are not self-replicating and do not spread in the manner of a disease (e.g. while considered biological and chemical agents due to their natural method of production, they are not living). Toxins are subject to the general purpose criterion under the Convention and two are in Schedule 1: saxitoxin and ricin. Historically, a third toxin - staphylococcal enterotoxin B - has also been weaponised.

106. Saxitoxin is produced by certain freshwater algae; it has a median lethal dose (LD50) estimated to be about 2/3 of the comparable dose of the nerve agent VX. Ingestion of saxitoxin, usually by consumption of shellfish contaminated by toxic algal blooms, is responsible for paralytic shellfish poisoning (PSP). PSP causes weakness, staggering, loss of muscle coordination, difficulty in swallowing, laboured respiration, muscle paralysis, death, tingling around the mouth or fingertips, and slurred speech. No antidote exists for saxitoxin poisoning, making supportive care the only treatment option.

107. Ricin is a potent cytotoxin (toxic to cells) that occurs naturally in the castor bean. Symptoms of ricin intoxication include fever, cough, nausea, chest tightness, sweating, cyanosis, hypotension, and dyspnoea (laboured breathing). Ricin can induce circulatory and respiratory collapse within 36-72 hours of exposure, leading to death. The mortality rate of ricin poisoning is about 85%. Ricin vaccines have been developed, but their commercial availability is at least three years away. The observed symptoms of ricin poisoning by inhalation can resemble those associated with pneumonia.

108. Staphylococcal food poisoning is one of the most common food-borne diseases, a result of ingestion of staphylococcal enterotoxins (SEs) in food, produced by the bacterium staphylococcus aureus. More than 20 SEs have been described. Staphylococcal food poisoning outbreaks are characterised by the identification of S. aureus biovars and their biomarkers using immunodetection and mass spectrometry

[18] See for example, the United States Department of Homeland Security Chemical Facility Anti-terrorism Standards Chemicals of Interest List; https://www.dhs.gov/publication/cfats-coi-list.

(MS). Availability of reference materials is critical to avoid misinterpretation of food poisoning events, and to assist emergency responders and decision makers.

109. Toxins exert diverse functions in human cells, yet have several commonalities.

(a) Detection of high molecular-weight protein toxins is a challenge, as the molecules are active in the absence of the producing organism, and do not contain genetic material. Therefore, the proteins themselves have to be detected.

(b) High toxicity necessitates low detection limits, especially for the analysis of clinical samples.

(c) Toxins are often produced in numerous variants or isoforms that can differ in chemical properties. Methods must be available to distinguish them precisely. From an analytical perspective, it is important to ensure that no toxic variant evades recognition.

110. A range of detection and identification methods for toxins have been developed by expert laboratories. Key problems include lack of certified reference materials, lack of accessibility of high-quality detection tools and materials for validation purposes, the absence of commonly accepted standard operating procedures, and a lack of regular proficiency tests (PTs). As a result the comparability of different methods is currently limited. Some of these issues are to be addressed by the European programme for the establishment of validated procedures for the detection and identification of biological toxins (EuroBioTox), which involves 23 European laboratories and began in June 2017.

111. The SAB commends the OPCW for initiating biotoxin analysis exercises. The objectives of these exercises are to improve capabilities for analysis; work toward recommended methods; establish a framework, including reporting, identification, and evaluation criteria for future PTs; assess the advantages and disadvantages of different analytical methods; and develop acceptable criteria for the identification of biological toxins, where biological functionality may need to be characterised.

Recommendations

112. The SAB's ricin and saxitoxin fact sheets (SAB-21/WP.5, dated 28 February 2014; and SAB-21/WP.4, dated 28 February 2014 respectively) should be revised by the Secretariat in collaboration with experts from designated laboratories (DLs), and supplemented with additional fact sheets that summarise information on other toxins deemed to pose a potential risk to the Convention.

113. Standardised methods for identification and analysis of saxitoxin and ricin should continue to be developed. The Secretariat would benefit from building an international capability to analyse samples containing these Schedule 1A chemicals.

114. Methods for identification and analysis of other toxins that have been weaponised, or pose a high risk of use as chemical weapons, should be considered for inclusion in future biotoxin exercises.

115. Sample preparation for the identification of toxins in difficult matrices must be addressed if low detection limits for toxins are to be achieved. Development of certified reference materials should remain a priority.

116. Given the diversity of needs and expertise in toxin identification and analysis, the SAB recommends that the OPCW Laboratory and the DL network engage with other networks of laboratories having toxin expertise to share best practices.

Bioregulators

117. Bioregulators are endogenous chemicals that mediate a range of life processes, including control of blood pressure, airway compliance, and functioning of the gastrointestinal system. In the brain, they modulate sleep, mood, cognisance and behaviour. They encompass a wide range of chemical classes, including peptides, small proteins (polypeptides comprising up to approximately 50 or more amino acids), nucleotides, lipid-derived metabolites, and small molecules such as neurotransmitters. Bioregulators were previously considered by the TWG on the convergence of chemistry and biology.

118. No data have been published that suggests that any individual CNS-active peptide should be regarded as a chemical of concern. Naturally-occurring peptides are usually rapidly metabolised and are poorly absorbed through biological membranes such as the lung and the blood-brain-barrier (BBB). They can be chemically modified to increase their potency and toxicity, resulting in extra complexity and cost. Advances in nanotechnology could potentially help transport bioregulators across the BBB, overcome host defences, and target specific organs. Some peptides that cause bronchoconstriction by interaction with receptors on the surface of the lung have been reported to have moderate to high inhalation toxicity in small rodent species.

Recommendations

119. As concluded by the TWG on convergence, the SAB views that the potential of peptides for development as incapacitating agents may have been overstated by some commentators. Peptides could be produced using metabolic engineering and synthetic biology but the pharmaceutical industry currently regards chemical synthesis, using specialised equipment, as the most cost-effective method for producing small peptides. The threat of possible misuse of this technology with regard to the Convention is currently considered low.

The Annex on Chemicals

120. As noted in the SAB's report to the First Review Conference (Annex to RC-1/DG.2, dated 23 April 2003), some chemicals listed in Schedule 1 were developed during the 1940s and 1950s, while other Schedule 1 chemicals are even older. As the Fourth Review Conference takes place, all chemicals listed in Schedule 1 have now been in the public domain for more than 35 years. Consequently, the current schedules do not

contain any new CWAs that may have conceivably emerged during the past decades. Also, they do not take into account other highly toxic chemicals that are potential candidates for weaponisation. Including chemicals in Schedule 1 only when past weaponisation and/or stockpiling is a known fact, or when highly toxic compounds have no legitimate uses, carries the inherent risk that the OPCW and its State Parties could be caught by surprise, should any unscheduled chemical(s) be used as CWAs.

121. A review of TICs, salts of scheduled chemicals, CNS-acting chemicals, bioregulators, toxins and unscheduled chemicals determined to pose a risk to non-proliferation might highlight chemicals that might be considered for inclusion in the Schedules should their updating be recommended. This might aid in the prevention of re-emergence of chemical weapons once destruction of declared stockpiles has been completed. The SAB notes that the Convention, through Article XV, contains a mechanism to amend the Schedules. This mechanism allows chemicals to be added to, deleted from a Schedule, or moved from one Schedule to another.

DEVELOPMENTS IN CHEMICAL PRODUCTION

Industry

122. Modern industrial chemical production processes increasingly including automation and digitalisation ("Industry 4.0") to improve process control and integrate safety standards and regulatory requirements. This is true for efforts in chemical discovery as well as manufacturing.

123. Safety–by-design and quality-by-design, and robustness testing using Design-of-Experiments (DOE) methodology, are commonly used to develop pharmaceuticals. Adoption of analytical technologies (typically spectroscopic) incorporated into production processes are seen as future directions in pharmaceutical manufacturing.

124. Shortening of time-to-market for pharmaceutical products (which is typically 10 – 15 years for drugs) offers a significant competitive advantage. Technologies for pharmaceutical production that significantly extend the development process due to additional validation requirements are unlikely to be adopted.

125. Similar considerations on time-to-market may apply to new synthesis technologies (including continuous flow), where any additional time to develop a manufacturing system, versus using equipment that is already well characterised, could slow adoption. In general, new technologies for pharmaceutical manufacturing are expected to be introduced in conjunction with new products, as changes to existing products would require revisiting validation to satisfy regulatory requirements, unless there is an absolute need (e.g. to improve safety).

126. Highly active pharmaceutical ingredients (HAPIs) are prepared in complex production facilities built to safety standards suitable to the physiological activity and toxicity of the materials produced. HAPI production plants can resemble Schedule 1 facilities, but due to their production profile, may not fall under the Convention declaration threshold for discrete organic chemical (DOC) producing facilities.

127. Knowledge management within companies and amongst producers and developers is important and in many cases required under regulatory frameworks. Digitalisation provides opportunities for more efficient use of information and existing knowledge to be better integrated into chemical manufacturing.

128. Transferable learnings from industry can be valuable to areas relevant to the Convention; e.g. trace analysis, and risk assessment. For the latter, tools and chemical datasets have been developed to facilitate safer process and product design, and for compliance with regulatory frameworks. These tools may be relevant to those personnel engaged in chemical safety and security.

129. Looking at the impact on the Convention for verification purposes, inspectors should have up-to-date knowledge of processes and chemistry related to the schedules. Engagement with experts from industry and a more frequent review of industry-focused research and development would benefit the Secretariat and the science review process.

130. Greater levels of science and technology engagement, and knowledge sharing amongst States Parties, could also support the verification regime through the increased transparency such initiatives bring.

131. Adequate levels of scientific understanding will remain critical in making any assessment of an industrial capability or facility; unusual practices cannot be recognised without adequate knowledge. In this regard, given the dynamic nature of the global security environment, the SAB notes that discussion of the fitness of the current schedules may be warranted (see also paragraph 121).

Recommendations

132. The changing nature of chemical production in industry was considered by the SAB in its TWG on Verification, from where the following advice originated:[19]

(a) Not all facilities that fall under Part IX of the Verification Annex should be considered of the same relevance to the object and purpose of the Convention. In this regard, a practical approach for enhancing the utilisation of verification resources for OCPF declaration and on-site inspection processes might be considered by the Secretariat and the policy-making organs. This could include exempting certain OCPFs from declaration requirements based on risk assessments, product/precursor and industry sector considerations.

(b) An increasing number of facilities produce DOCs which may have relevance to the Convention (for example HAPIs and toxins used in cancer therapy) at low production volumes. In this regard, the verification thresholds for OCPFs producing highly relevant chemicals, and the possibility of revision of the

[19] These recommendations were adopted from recommendations 9 and 10 of the TWG on verification as discussed in SAB/REP/1/15, dated June 2015.

product group codes, should be addressed by the SAB as well as the industry cluster.

(c) The Secretariat could reassess which product group codes are highly relevant to the Convention. Facilities declared with these product group codes would be subject to a higher probability to be selected for inspection (which is consistent with the approach used in the A15 site selection algorithm). For facilities in product group codes that are considered less relevant, the Secretariat should identify appropriate mechanisms to augment the declared information with validated and credible sources to allow for an assessment regarding the need for on-site inspection.

133. The SAB notes that ensuring that the verification regime remains fit for purpose benefits from more extensive engagement with technical experts from industry, and review of industry-focused research and development, to stay adequately informed of developments. This augments the science review process and allows recognition of deviations from predicted trends.

134. Greater engagement with National Authorities could provide greater assurance on the accuracy and completeness of declarations. The SAB recommends visits to National Authorities as a complement to on-site inspections, as described in the report of the TWG on Verification.[20] This would allow the OPCW to undertake a review of National Authorities data collection and other declaration-related activities. The result of such visits could provide the basis for targeted support from the Secretariat to the National Authority. With time this would develop into more formal audit-type visits. The frequency and duration of such visits could be a function of the number and types of Article VI facilities declared. The assurance provided through the increased information exchange with the National Authorities could eventually lead to a reduction of the frequency of on-site inspections of declared facilities.

Chemical synthesis of biologicals

135. Substances of biological origin (biologicals) include nucleic acids (e.g. DNA or RNA), proteins and peptides, lipids, carbohydrates, and materials and small molecules that can be produced by chemical methods.

136. Nucleic acid production by chemical synthesis is an established practice to provide material for genetic modification of microorganisms (which are then used to develop biomediated production processes). The synthesis of small peptides can be performed cost-effectively, but requires specialised equipment. Non-protein toxins (like saxitoxin) are more likely to be isolated from natural sources as chemical synthesis is impractical due to their complex molecular structures. The synthesis of large proteins by chemical methods is limited in scalability (typically only milligrams are prepared)

[20] These recommendations were adopted from recommendation 6 of the TWG on verification as discussed in SAB/REP/1/15, dated June 2015.

and biomediated processes, or collection of these materials from the organisms that produce them (microbes, plants, animals), are often more practical.

137. Technical capabilities exist for the synthesis of toxins, bioregulators and other physiologically active peptides. However, the misuse of such technologies to produce large quantities for weapon purposes is thought impractical. Acquisition of such materials by non-State actors would likely be through natural sources rather than biotechnological means.

<u>Recommendation</u>

138. Risk assessments of bioregulators and toxins as weapons may be useful to consider. Understanding the potential misuse of such materials would be helpful in supporting the prevention of re-emergence of chemical weapons.

Biological production of chemicals

139. Adoption of biological production methods in commodity and fine chemical sectors has fallen short of predictions made at the Third Review Conference. This has been partly due to chemicals produced through biomediated processes being more expensive than those produced from petrochemical feedstocks a consequence of low oil prices over the last few years. Adoption of biomediated processes in the specialty chemical sector has increased, with commercial uses of synthetic biology finding application to flavours and fragrances.

140. Many terms are used to describe processes that enable biomediated production of new chemicals (metabolic engineering, synthetic biology, gene editing, directed evolution, and more). The SAB advises consideration of these as a collection of approaches that can be used to develop microbes capable of producing chemicals, rather than separate and unconnected fields of science.

141. A variety of complex proteins (including enzymes and antibodies) with therapeutic uses (biosimilars) are known. Enzymes are produced for catalysis and as decontaminants. Proteinaceous biological materials can be of commercial interest (e.g. a company commercialising synthetic biology produced spider silk).

142. Genetic modification of microbes to produce toxins is not required if the materials are obtained from natural sources, e.g. ricin from castor beans and botulinum (produced commercially for anti-wrinkle cosmetics) from the anaerobic bacteria that naturally produce it. The SAB notes that while commercially developed protein production technologies can produce protein toxins, process development requires appropriate resources and expertise. When engineering natural microbes with modified genomes to produce a toxin (and/or other metabolic products), compatibility of altered genomes, as well as the toxin products in host cells, is required. Current capabilities to predict compatibility are limited and commercial operations have developed large scale automated screening platforms for screening many thousands of modified microbes for functionality.

143. The use of microrganisms (particularly algae) that can consume waste gases such as carbon dioxide and methane as feedstocks to produce more complex chemical

products has been demonstrated (for example, the "LanzaTech Process"). This technology allows waste gases from sources that might include cement plants or refuse disposal sites to be captured and used to produce chemical products. These technologies in principle could allow the development of decentralised chemical production business models. Their future adoption may be influenced by efforts to become carbon neutral.

Continuous flow chemistry

144. Continuous flow reactors enable the production of chemicals. These modular units can be connected in series or in parallel, and can incorporate in-line analytical equipment (to enable the analysis of reaction intermediates and to confirm conversion into the desired product/s). They are being used increasingly for chemical discovery. Modular automated approaches to chemistry are not new, having been successfully applied to coupling chemistries for producing nucleic acids and peptides for many years. However, advances in flow chemistry systems are permitting a greater diversity of chemical reactions to be performed reproducibly. Flow reactors can offer new ways to perform chemical transformations and reduce chemical handing and reaction-related safety risks (the systems use small amounts of chemicals).

145. Linking sets of flow reactors allows multiple pharmaceuticals to be produced by a single system. Chemistry can be performed simultaneously under a variety of reaction conditions that can be adopted in subsequent reactors (for further transformation); products can be isolated in high purity through in-line work-up/biphasic extraction. These approaches might enable capabilities for laboratories to quickly generate large sets of analytical data, screen for reactivity and toxicity properties, and elucidate degradation pathways of a broad range of chemicals. Recent developments in continuous flow reactors include demonstration of the potential capability to work with solids (through the use of sonication to move solid particles and encapsulation of particles in microbubbles), integration of photochemical and microwave reactors, *in-situ* formation of reactive intermediates (including singlet oxygen), and the ability to generate products that can be immediately characterised through interfacing the continuous flow systems with mass spectrometers.

146. Flow reactors could potentially be used to produce small quantities of CWAs combinatorially or CWA derivatives on demand, making them potentially useful for synthesising analytical standards. There are potential disadvantages also, e.g. leakage or potential blockage by solids precipitating, both of which could impact on safety. Tolerances of the system(s) would need to be understood and procedures adapted for routine use. Such problems would also need to be overcome for any potential misuse of these technologies to produce toxic chemicals clandestinely. The SAB notes that the use of microreactors (which are also continuous flow systems) to reduce the footprint of a system that is making CWAs remains of concern. However, traditional laboratory bench-scale chemical equipment (e.g. glassware) would also present a small footprint that could be concealed for preparing small amounts of material and the equipment later disassembled.

147. Coupling continuous flow reactors to analytical instruments and chip-based assay platforms would enable real-time synthesis and activity screening of new compounds.

With suitable development, such systems could be used to screen toxicity (e.g. coupling to an "organ screening chip") or material reactivity (which could provide information on reactivity of an industrial chemical to inform sample collection in an investigative mission). The Secretariat might consider how continuous flow systems that allow screening of reaction conditions, reactivity and/or toxicity screening of materials or reagents could be used within the OPCW Laboratory and its DLs.

148. Continuous flow systems are used for industrial-scale chemical production. These are typically large systems optimised for dedicated production of a specific product.

Additive manufacturing

149. Additive manufacturing (3D printing) has developed tremendously in the past few years and is excellent for fast prototyping of equipment as well its repair. 3D printers have been used to produce laboratory supplies (tools and disposables), flow (and micro) reactors, uniform micro-particles, formulations (e.g. for pharmaceuticals), and structured biological materials (through printing on different types of cells) that include artificial organ prototypes. Issues impacting the use of 3D printing in chemical laboratories that would need to be considered include the reliability and tolerances of printed parts, contamination (and potential interference with chemical and biological samples) from chemicals leaching from the plastics used for printing, and material compatibility (printing metal parts is possible, but may require expensive and optimised printers). The possibility of additive manufacturing for providing industrial equipment and critical high-performance items (e.g. chemical reactors) would need to be assessed in a laboratory before adoption into practice.

150. A potential application is printing on-site consumables, small parts and some lab equipment. Plastic materials and a printer are required, "recipes" can be programmed into the printer or received virtually (this has been demonstrated by printing mechanical tools on the international space station from recipes emailed from Earth). Panels and parts that enable construction of structures (e.g. containment cabinets and/or storage sheds) have also been demonstrated with suitably-sized and material-compatible 3D printers. This could provide potential for flexibility in capabilities for an on-site mission in future if easily transportable and fast printing systems become available (long printing times are currently a limitation).

151. Security risks of 3D printing have also been discussed, especially the ability to print conventional weapons. In regard to preparing chemicals, 3D printers do not appear to offer benefits over traditional (and more capable) methods, but they can be used to prepare chemical formulations (e.g. tablets and nanoparticles that could contain toxic substances) and specialised laboratory equipment for chemical synthesis (e.g. flow reactors). The ability to print lab equipment may decrease the barrier to setting up illicit or clandestine laboratories. It is also conceivable that spraying equipment or other chemical delivery devices could be produced by 3D printers. Advances in 3D printing relevant to chemistry should continue to be monitored.

TECHNOLOGIES FOR THE DELIVERY OF TOXIC CHEMICALS AND DRUGS

Status at the Third Review Conference

152. The development and commercial availability of munition systems capable of delivering large quantities of RCAs over large distances, devices for the dissemination of chemical and biological warfare agents by non-State actors, and spray and fogging devices developed for agriculture or large-scale veterinary treatment of animals, were identified as areas of concern.

153. Methods of drug delivery being developed in the pharmaceutical industry, especially administration of drugs by inhalation in the form of respirable aerosols, which might be exploited for delivery of CNS-acting chemicals, were reviewed. It was noted that the methods developed and optimised for targeted drug delivery may not be easily transferable to, or suitable for, offensive CWA delivery.

Munitions and spraying devices

154. The continued development, testing, production and promotion of diverse munition systems capable of disseminating RCAs by remote control remains of concern, as these systems could also enable the delivery of toxic chemicals. Such delivery mechanisms include fixed indoor devices, external area clearing or area denial devices, grenade and multiple munition launchers, and delivery systems on unmanned ground and aerial vehicles (UGVs and UAVs). The availability of such systems opens up the possibility that they could be filled intentionally with alternate types of chemicals including CWAs or CNS-acting compounds.

Drug delivery

155. The development of more effective drug delivery systems continues unabated. Antibody drug conjugates (ADCs) have been developed and tested for the targeted delivery of cytotoxic payloads to cancer cells. Producing ADCs requires expertise in chemistry, biology and immunology, and production in bulk quantities has been demonstrated. In terms of capacity, reactor sizes can vary from small (6 to 60 litres) to large (up to 600 litres, batch sizes up to 3 kg). Given the high toxicity of the cytotoxins used in the ADCs, ADC production facilities are characterised by high containment, the use of isolators and safety hoods, and rigid standard operating procedures, analogous to HAPI manufacturing facilities.

156. Current production volumes of ADCs fall below declaration thresholds. However, there is potential to increase batch sizes and scale up processing equipment. It was noted that the amounts produced are intended to match market demands and quality of product is emphasised over quantity of material produced. In future, as healthcare may shift toward personalised medicine (some developments in this area are currently in use), small batch manufacturing of a diverse range of medicines tailored to the requirements of individual patients might be expected.

157. Nanoparticle-based formulations (nanocarriers) are being explored in medicine for enhanced or 'smart' drug delivery. Examples include controlled drug release,

enhanced penetration of the BBB (e.g. for therapeutic peptides), and targeting specific organs or cells (with the majority of drugs being developed for cancer cells). The types of nano-particles most commonly used in drug formulations include: imprinted polymers, dendrimers, vesicles, nano-spheres, nano-capsules, micelles, liposomes, and nano-mulsions. Additional bio-based nanocarriers are being researched including DNA- and virus-based systems. These nanocarriers can comprise a variety of materials (e.g. organic, mineral, and composite) and architectures (e.g. spheres, rods, and tubes).

158. Nanocarrier-based delivery systems present several advantages to traditional drug delivery approaches, in particular: overcoming solubility problems, protecting the drug from the environment (temperature, photo damage, pH), and controlling its release profile. These delivery systems permit more precise and controlled targeting at the site of action, while reducing the time of exposure of non-targeted tissues. This can potentially increase efficacy, and reduce toxicity and side-effects.

159. In terms of respiratory inhalation drug delivery systems for medical treatment (e.g. for tuberculosis), a recent review classified nanotechnology-based drug-delivery systems into four groups:

(a) solid-lipid particulate delivery systems based on solid-lipid micro and nanoparticles;

(b) emulsion based delivery systems using micro- and nano-emulsions;

(c) vesicular and micellar drug delivery systems; and

(d) a miscellaneous group accommodating micro and nanoparticles, as well as polymeric nanoparticles, dendrimers, carbon nanotubes, quantum dots and nano-suspensions.

160. The enhanced delivery of therapeutic drugs to their biochemical target could be exploited for the delivery of toxic chemicals to humans, although there is a considerable difference between a chemical weapon and a high value pharmaceutical. The SAB notes that technological progress in pharmaceutical science does not automatically produce non-proliferation risks (individual drugs, their mechanism of action, cost and production volumes, and route of delivery would need to be assessed on a case by case basis).

SCIENCE AND TECHNOLOGY OF RELEVANCE TO VERIFICATION

Overview

161. The SAB's TWG on verification considered opportunities arising from technological change for ensuring the Secretariat's verification activities remain fit for purpose, and was of the view that particular attention should be given to remote/automated monitoring equipment, satellite imagery and information analysis tools. The Secretariat was encouraged to stay abreast of industrial developments relevant to the implementation of the Convention. In regard to technologies with applications for

verification, instrument portability and miniaturisation were identified as enablers for on-site sampling and analysis.

162. Effective verification is not the assessment of an individual data point as the outcome of an inspection, but rather all relevant data points pertaining to the site and State Party. To be able to better understand the effectiveness and completeness of the implementation of the Convention, the Secretariat was encouraged to move towards a comprehensive systems-based approach where all the separate elements of information are combined and analysed systematically. The SAB therefore recommended that the Secretariat considered adopting a comprehensive, more analytical approach to verification utilising all available and verifiable information, noting that:

(a) Adopting a more analytical approach to verification would require adjustments in the management and handling of information. It will also have organisational implications, as the collaborative analysis of information will require a more transverse or matrix-based organisation throughout the Secretariat to enhance potential synergies and make the best use of competences and expertise.

163. Effective use of data analysis, data mining, statistical analysis, and attribution analysis would serve to enhance existing capabilities for verification purposes. In this regard the SAB recommended that the Secretariat put in place an information management structure that could provide the support required for the verification process, with the understanding that a more analytical approach to verification, using all available information (declarations, inspection reports, satellite imagery, open source information, and any other pertinent data), would require improved information management support. As part of this effort, the Secretariat should undertake a review of the Verification Information System (VIS), develop new templates for Article VI inspection reports that would allow the uploading of the entire report as a searchable document to the VIS, and explore possibilities for the application of secure electronic transmission of documents and data between the inspection site and OPCW Headquarters.

164. The SAB reiterates the previous recommendations and also recommends that remote and/or automated monitoring technologies be added to the list of approved inspection equipment. These technologies are well suited for conditions where physical access is difficult and would help to optimise the use of resources: examples of such technologies used successfully, in the OPCW-United Nations Joint Mission on the elimination of chemical weapons in the Syrian Arab Republic, include “smart” seals, cameras with remote data transmission capability, and other sensor platforms.

165. The SAB further recommends the Secretariat considers the option of using satellite imagery for the planning of non-routine missions, in particular for IAUs and challenge inspections (CIs). Training and familiarisation of how to best utilise satellite imagery could be valuable to include in IAU and CI exercises. The SAB also recognises that satellite imagery could be used for routine inspections, where access to the site is difficult due to security concerns. The Secretariat may consider cooperating with other international organisations/specialist agencies to enhance

capabilities in the use of satellite information (particularly hyperspectral and non-visible light imagery).

166. In the view of the SAB, analytical procedures and protocols should be reviewed to ensure flexibility to handle different sample types, large sample numbers, and to accommodate short time-frames whilst ensuring robust analysis and reporting. Lessons learned from contingency operations in the Syrian Arab Republic have been important in shaping the analytical requirements that may be needed for future non-routine operations.

167. Furthermore, the SAB recommends that the Secretariat should keep a watching brief on innovations relevant to chemical analysis and/or chemical forensics. The findings of the TWG on investigative science and technology can also contribute.

Analytical instrumentation

<u>Status at the Third Review Conference</u>

168. Recommendations were made for methods to detect ricin and saxitoxin by screening techniques with confirmation by liquid chromatography tandem mass spectrometry (LC-MS-MS). Advances in analytical instrumentation with improved capabilities for Convention-related analysis such as nuclear magnetic resonance (NMR) spectroscopy for aqueous samples and complex mixtures, Raman spectroscopy for chemical detection and identification, and high resolution mass spectrometers capable of accurate mass measurements, were noted. The importance of capabilities for accurate mass measurements that allow determination of molecular formula of compounds not included in the OCAD and with application for the analysis of proteinaceous toxins was also documented.

169. Confirmation of nerve agent exposure in biomedical samples relies on gas chromatography (GC), or LC combined with MS-MS or high resolution mass spectrometry (HRMS). Nerve agent biomarkers fall into main groups: free metabolites and adducts. Metabolites are detectable for a short period in urine (up to several days) and have a shorter lifetime in blood.

170. In terms of methods and equipment for detecting CWAs, advances in miniaturisation using technological approaches such as nanotechnology were mentioned. However, a lack of selectivity, cross-reactivity (leading to false positive identifications), and insufficient robustness, were observed for many of the techniques available at that time, making them unsuitable as standard methods. Progress and improvements were however anticipated.

171. NMR spectroscopy and MS were recognised as tools that could be used to obtain data with forensic value, such as impurity profiles and isotope ratios (this had been demonstrated in a number of fields of chemical analysis, and a several studies related to the potential use of these approaches for CWAs had been published).

On-site analysis and recommendations

172. Instruments continue to be developed that are smaller, more portable and in the case of biosensors disposable. These instruments may help reduce the logistic burden of on-site analysis. Developments in analytical instrument portability, miniaturisation and disposable biosensors, should be reviewed periodically by the Secretariat and the SAB for potential applicability to on-site analysis.

173. Portable GC- and LC-MS instrumentation and direct sampling MS techniques, such as Desorption ElectroSpray Ionization (DESI) and Direct Analysis in Real Time (DART), which both eliminate the need for sample preparation, continue to improve. These direct sampling techniques have the potential to extend the range of analytes that could be determined on-site. DESI is already being used for Convention-related analysis in some mobile laboratories.

174. Miniaturisation of mass spectrometers for applications in defence and security, and for first responders and in the pharmaceutical industry, continues. Instruments based on time-of-flight or ion trap technologies have become commercially available (with others in development). These instruments have small dimensions and a low weight (< 15 kg), allowing rapid transportation for on-site use, and some of these may not require specially-trained operators.

175. MS-equipped UAVs have been developed and are relevant to non-compliance related investigations. Such systems can make measurements of molecules in the 100-200 amu mass range (typical of many CWAs and scheduled chemicals). These might allow the detection of scheduled chemicals in the air. A UAV with a 12 kg payload, 1 h flight time, 3-5 km range, and automatic take off/landing capability, could be customised with sampling capabilities, and deployed from afar. Using such systems could help to ensure the safety of OPCW personnel collecting evidence in hostile or contaminated environments.

176. Remote/automated monitoring technologies should be added to the list of approved inspection equipment. The use of small and compact systems that incorporate a diverse range of analytical tools, conceptually similar to those integrated into robotic systems such as Mars Rovers, could play an important role in on-site analysis. The OPCW could build on currently existing technologies to incorporate other portable devices in rover-type mobile devices and/or drones. The Secretariat might engage with experts developing environmental robotic monitoring systems.

177. Rugged hand-held instrumentation based on Raman spectroscopy is available and has been used by the Secretariat during the mission to remove chemicals from the Syrian Arab Republic. Raman spectroscopy can be used for a variety of chemical sample types; it offers the capability to allow measurements to be taken through semi-translucent sealed containers and directly on aqueous solutions and white- or light coloured-powders. Similarly, portable Fourier transform infrared spectroscopy (FTIR) can be used for various measurements on coloured and fluorescent powders, providing complementary data to Raman spectroscopy. Both techniques can be used to identify CWAs, their precursors and other Scheduled chemicals, but are limited to

pure compounds and simple mixtures. User expandable spectral libraries are available with commercial instruments.

178. The Secretariat should remain aware of developments in on-site analysis tools that can provide preliminary detection and an indication of where to collect samples for subsequent off-site analysis. Examples of such tools available to inspectors are the CALID paper colorimetric test and the handheld chemical agent monitors, such as the LCD-3.3 (an ion mobility mass spectrometer). The SAB notes that a variety of handheld devices are routinely used in other fields of expertise (these include spectroscopic capabilities, and sometimes MS, and, for non-destructive chemical identification, X-ray diffraction or X-ray fluorescence). The Secretariat might consider its needs for on-site chemical analysis and evaluate scenarios that could benefit from such detection advances, including consideration of the equipment capabilities required under such scenarios.

179. Published reviews provide additional information on hand-held CWA detection devices which increase understanding of their limitations and the ability to recognise false positive and negative readings that are required for their efficient use. For increased safety, a combination of detectors can be used to maximise the chances of detecting CWAs during reconnaissance or sampling operations.

180. Networks of electronic nose (eNose) devices are used for gas sensing in mines and industrial sites (chemical refineries and ports), and detection of explosives. Wireless communication coupled with eNose systems enable the monitoring of airborne chemicals. Combined with geospatial and temporal data acquisition, they allow modelling of gas clouds and their movement in real-time. Low installation and maintenance costs, compared to conventional chemical monitoring systems, are one advantage. The components of eNose devices comprise low cost metal-oxide gas sensors. Use of eNose devices requires the availability of datasets of chemicals of interest. It is also possible to fit UAVs with commercial eNose devices designed for environmental and industrial monitoring. Medical diagnosis through breath testing is another area where eNose technologies are seeing adoption. With suitable datasets, on-site and mobile clinical health assessments may be possible.

181. A review of point-of-care detection options for toxins and other CWAs - such as lateral flow and paper-based devices - would be valuable to first responders and OPCW inspectors. The SAB suggests that developments in, and availability of portable and disposable biosensors, be monitored.

182. Immunological assays employing high-affinity monoclonal antibodies have been used for on-site detection of biological toxins, with limits of detection at single digit pg/mL levels being possible. Over 70 high-affinity monoclonal antibodies have been generated for various biological toxins and used in immunoassay platforms.

183. Advances in NMR instrumentation include fieldable instruments with the capability to identify chemical structures in unknown samples, using J-coupling signature detection in ultra-low magnetic fields (using the Earth's magnetic field or a low magnetic field electromagnet). Combining ultra-low magnetic field (ULMF) capabilities with dynamic nuclear polarization (DNP) enhanced J-coupling NMR spectroscopy

provided a portable system for detecting CWAs, precursors and related compounds, in non-ferrous metal containers.

184. Inorganic impurities in a chemical sample (originating from production equipment and/or storage containers) may have forensic relevance. For example, boron and strontium isotopes can indicate of the types of glass a chemical may have been in contact with. Likewise, materials used in munitions (shell casings and energetic materials) could also have characteristic inorganic signatures. Portable X-ray fluorescence equipment, such as those used in art analysis, might quickly provide on-site information on inorganic impurity profiles.

<u>Off-site analysis and recommendations</u>

185. The most important development in MS instrumentation in recent years has been the availability of routine HRMS which is now available in several DLs and provides substantial advantages for off-site analysis. The technique facilitates the determination of the molecular formula and structure of "unknown" analytes (this is especially relevant for analysis of compounds for which no data is available in the OCAD or NIST databases). HRMS additionally allows retrospective trace analysis through post-acquisition searching of full spectral data.

186. The sensitivity of the off-site analysis methods available to OPCW and the complexity of the samples these methods are capable of analysing is illustrated by the detection of chemical agents, their breakdown products and microbial metabolites, from Baltic Sea sediments, and in sentinel species such as mussels collected in the vicinity of sea-dumped CWAs.

187. The SAB views the development and validation of analytical methods for toxins to be of utmost importance for capabilities of laboratories engaged in the implementation of the Convention. The development of MS, immunoassay and other bioassay methods through the EQuATox project and OPCW Laboratory biotoxin exercises has been highly valuable. The SAB encourages the Secretariat to continue these activities and develop in-house capabilities and collaborations with relevant networks of experts.

188. Whole-cell Matrix Assisted Laser Desorption/Ionization Time-Of-Flight (MALDI-TOF) methods have been developed for pathogen and toxin identification. A one hour MS measurement, allowing the identification of several thousand peptide sequences, can provide an overview of the microbiota and identify the presence of pathogenic species in complex samples. These proteomic tools are being developed for applications in chemical and biological disarmament and defence, human health and environmental monitoring.

189. Note was taken of the potential of Site Specific Natural Abundance Isotope Fractionation (SNIF)-NMR as a quantitative tool to utilise site-specific natural abundance stable isotope ratios at each accessible carbon or hydrogen in a CWA to relate the site-specific information to precursor chemicals and reagents. These developments are relevant to the use of NMR spectroscopy for chemical forensics purposes.

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190. Advances on the utilisation of ^{1}H, ^{31}P, ^{19}F-quantitative NMR (qNMR) technology to determine and quantify the amount of various biotoxins, such as those originating from marine organisms, with greater accuracy and precision, is also noted. This technology relies on the use of an internal or external referencing system to accurately calculate the amount of toxin in solution.

Recommendations for additional methods with potential applications to on- and/or off-site analysis

191. Paper spray MS (PS-MS) is another method suitable for direct analysis of CWAs in biological and environmental samples. PS-MS is an ambient ionisation technique that does not require purified ionising gas. Paper spray cartridges have been coupled to high resolution, tandem and miniaturised MS systems. The method offers rapid analysis time, low limits of detection, and little or no sample preparation.

192. Developments in the combination of ion mobility spectrometry (IMS), already used in instruments for on-site analysis of CWAs, with gas chromatography (GC-IMS) and MS (IMS-MS) can also improve qualitative and quantitative analysis of CWAs.

193. Developments in PS-MS, GC-IMS and IMS-MS should continue to be monitored and the Secretariat might consider opportunities for field evaluation.

Remote monitoring and sensors

Overview and recommendations

194. The SAB notes that given advances in capabilities to gather, integrate and analyse diverse sets of data, particular attention should be paid to remote and automated monitoring equipment, satellite imagery and any complementary measurements (e.g. geospatial and temporal data). The use of equipment such as seals, cameras with remote data transmission capability, UGVs, UAVs, and sensor platforms for on-site monitoring could be considered as suitable additions to the list of approved equipment identified by the Secretariat.

195. The International Atomic Energy Agency (IAEA) has shown the benefit of use of seals with remote data transmission capability; such seals could potentially be used for on-site monitoring purposes in accordance with the provisions of the Convention. The application of these technologies may reduce the need for the on-site presence of inspectors and increase the efficiency and cost-effectiveness of verification activities.

196. The experience gained from the missions to the Syrian Arab Republic also demonstrated the value of remote and automated monitoring technologies. Such equipment can optimise the use of resources and provide alternate solutions for data collection in non-routine operating conditions where approved on-site equipment such as a HAPSITE® is unsuitable (when ambient conditions are outside the temperature ranges of operability for example). Remote sensing capabilities would also have applications under conditions that limit physical access or place personnel in danger.

197. Remote sensing technologies have seen dramatic advancements over the past decade, and allow access to vast amounts of information. Significant advances in the

capabilities of these technologies are coming from the study of terrestrial (and extra-terrestrial) ecosystems and precision agriculture. Of relevance to the implementation of the Convention are capabilities that allow the detection and recognition of biochemical change in the environment.

198. In agriculture, remote and proximal sensing techniques combined with informatics and data have enabled the capability for early (and possibly real-time) detection and identification of plant diseases as well as indicators of chemical content. The most promising methods include thermography, chlorophyll fluorescence, and hyperspectral sensing. The available sensor systems can provide high-resolution imagery for crop stands or single plant organs. Optical sensing can be coupled with other analysers (e.g. eNose technologies) and data streams, to identify states of plant health that alert farmers to take action to mitigate crop yield losses. Observable physiological and phenotypic characteristics of plants have been related to molecular biological mechanisms and markers (using OMICS methods). Generating and understanding the datasets for imaging tools to be able to recognise characteristics and correlate to molecular effects would require generating and validating datasets. Mobile apps have been developed that allow photographs of individual plants to be analysed (using AI methods).

199. In regard to capabilities developed for agricultural purposes, the uptake of chemicals (in particular TICs) and chemically-induced damage (e.g. decolourisation and other effects induced by exposure to chemicals that include sulfur mustard, VX and chlorine gas) can also induce observable changes in plant health. Tools developed for agriculture and data-sets relevant to sensing of toxic chemical release have potential value in post-event fact-finding (for identifying where to collect samples or as indicators of a certain type of chemical exposure) and in real-time detection of chemical exposure. Plant-based biomarker (and associated adducts of reactive chemicals) could potentially provide a means for confirmation of presence and/or exposure to a given toxic chemical. Engagement with technology developers for agricultural applications to explore opportunities in this area could lead to enhanced capabilities for the Secretariat in the environmental sampling and analysis of a broad range of chemicals.

200. Large-area spectral imaging by satellites or aircraft can be used to identify chemicals. These include mineral compositions, nitrogen and/or phosphorus content of soils, water (and even pH of oceans and lakes), and atmospheric chemicals including gases. Applications of chemical monitoring that might have relevance to the Convention include the detection of leaks in gas pipelines and the monitoring of toxic chemicals (sulfur dioxide) produced by the intentional fire of the Al-Mishraq sulfur mine in Iraq in 2016. Dispersion models informed by the data collected on gas release and diffusion can be used to identify areas where high toxic gas concentrations may form after a chemical release and can be used to predict the diffusion and transport of gas clouds. This is valuable information for emergency responders and authorities responsible for the safety of civilian populations.

201. Advances in space-based sensor technologies are now capable of producing datasets with high spectral, spatial, and temporal resolution. Continuity and enhancements in the data record are enabled through linking multiple satellite programmes, adding

power to trend analysis of environmental change. Spectral enhancements, capable of collecting information with chemical signatures, include hyperspectral sensors that provide full spectral information for each pixel of an image, thermal imaging and near-field infrared capabilities. Miniature satellites (CubeSats) are becoming less expensive to build and launch, with commercial ventures deploying CubeSats in swarms. High resolution scans of the planet are being acquired with increasing frequency and imagery is becoming more accessible through commercial sources. Imaging capabilities employed by satellite systems are used in terrestrial sensing applications on aircraft, including UAVs (allowing a focused analysis of a defined area with real-time inputs).

202. The satellite imagery is also becoming more accessible, sources like Google Earth Engine and various space agencies provide a wealth of open access, data sets. The number of commercial providers is also increasing, especially with the increase in CubeSat companies. Available imagery includes hyperspectral, thermal and infrared data.

203. Non-proliferation researchers have used, and continue to develop methods for the use of satellite imagery, combined with other available data sources to map, geolocate and monitor facilities of concern. Much of the information is available through public and commercial sources. Capabilities in image analysis and data integration could prove valuable for non-routine inspections and investigations. Developing such skills would allow the Secretariat to be better positioned to evaluate claims and reports from non-proliferation research.

Wearable technologies and smart devices

204. Inward-looking (self-monitoring) and outward-looking (environment-monitoring) wearable sensors for CWA and biological agent detection are available. Enablers for these wearable technologies include miniaturisation and sensors, nanomaterials, robust flexible electronics, transdermal biological fluid extraction (including sweat sensors and microneedle technologies), microscale power supply, knowledge of biomarkers for chemical/pathogen exposure, and information storage and transmission capabilities.

205. Colorimetric indicators have been used to detect explosives and CWAs. These include enzymatic systems for detecting sulfur mustard and passive samplers (wrist bands or patches). The latter consist of polymeric materials that can adsorb chemicals for off-site laboratory analysis. Wearable devices, with colorimetric indication, could provide early warning of toxic chemicals, and be incorporated into protective equipment or skin patches. The SAB notes that colorimetric indicators are conceptually no different than current practices of inspectors applying CALID paper onto their protective gear so that a colour change indicating certain CWAs can be detected when the paper comes in contact with liquids in an operational setting.

206. Colorimetric indicators can be useful for rapid on-site testing; however these tests have lower sensitivity and selectivity than instrumental methods. Indication systems perceived useful to OPCW inspectors should be field-tested before they are suggested

as additions to the approved list of inspection equipment. Characterising interferences, and false positive and false negative rates, is useful.

207. Current limitations for inward-wearable sensor fieldability include identifying and obtaining stable and reversible (bio)chemical receptors, understanding relevant biomarkers in accessible body fluids, and cost. Additional challenges include the construction materials, energy supply, the analysis, communication, and acquisition of data, filtering interference from chemicals in the environment, data processing, and data security. Regarding power sources, strategies to power mobile devices using energy created by walking have been demonstrated. For chemical and biological security applications, researchers predict that useful applications are likely to be a decade away.

208. A wearable self-monitoring cholinesterase activity device would help detect nerve agent exposure, possibly before the wearer realises they have been exposed (which is a critical time to administer countermeasures). Point-of-care devices are available, although continuous and real-time cholinesterase monitoring is currently a challenge.

209. Wearables for sporting applications (monitoring health and performance of athletes) have driven many advances for collecting inward-looking readouts using health indicators. Non-invasive measurements that can be collected continuously are possible for several body functions, including heart rate, skin temperature, blood oxygen levels, and physical activity. Investigations of the ability of wearable sensors to follow physiological changes that occur over the course of a day, during illness and physical exertion, have been published. In one example, data from non-invasive monitoring revealed personalised differences in daily patterns of activities, and changes in response to particular environments (e.g. airline flights). These results indicate that information from non-invasive wearable sensors can be physiologically meaningful and potentially actionable.

210. Suitable wearable devices might provide early indication of chemical exposure, allowing the deployment of protective/medical measures at the earliest moments. These wearable devices could have applications for monitoring individuals working in remote and dangerous environments. Changes detected in non-invasive signals may not by themselves diagnose the specific health condition responsible for the onset of the changes, but they could serve as a trigger to seek medical advice or to retreat from a hazardous environment. The SAB notes that wearable fitness monitors are seeing adoption in pharmaceutical clinical trials where correlations between data readouts and specific health conditions may be characterised (research in this area is sometimes referred to as "digital health"). The Secretariat would benefit from staying abreast of developments and should pursue opportunities to test whether such wearables could be advantageous for health monitoring of OPCW inspectors, especially those engaged in operations where stress is a possible risk.

211. Devices that transmit data for monitoring health raise concerns of data security. Methodologies that use AI and disease-specific data can be packaged into transportable systems (such as smart phones, tablets or watches) that do not access uplink feeds during use. With suitable datasets, non-invasive monitoring can provide heath indications at the point of collection and be used for diagnosis of a specific

condition ("smart data"). Interpretation of the data by a medical expert would be required.

Unmanned vehicles (including for sampling)

212. As noted in previous sections of this report, a variety of chemical and physical sensor instruments can be mounted on UAVs.

213. Chemical analysis of volcanic plumes with UAVs carrying miniature mass spectrometers is one example dangerous environment monitoring through remote sensing. The UAVs are flown into volcanic craters as they emit toxic gases, which ae identified by the on-board instruments. Such technology has the potential to be able to detect and monitor CWA release, and detect CWA-contaminated areas, without requiring personnel on the ground.

214. The detection of toxic chemicals on surfaces is typically achieved by point detectors. UAVs equipped with chemical biological radiological and nuclear detection, identification and monitoring (CBRN-DIM) capabilities would permit measurements to be taken without exposing investigators to dangerous conditions. Systems using mass spectrometers and eNose technologies have been reported. UAVs can be fitted with sample retrievers for collection of air, water, or soil samples for off-site analysis. Sticky touch pads would provide a low-cost option for collecting soil, dust, or materials by transfer off surfaces. There are many reports and demonstrations of the types of systems described in this paragraph. However it should be noted that these systems require user development and customisation to optimise them for intended purposes.

215. For non-spectroscopic chemical detection, UAVs require careful design. Chemicals in the exhaust of gasoline engines can interfere with measurements, while the use of electric motors reduces flying time and a range. The mounting of sampling and detection systems must be designed so that interference by the down draft from rotor blades is avoided. Furthermore, as speeds which detectors move over surfaces increase, detection limits may suffer. In general, chemical data collected using UAVs are affected by weather (temperature, wind, humidity), the presence of interfering chemicals, the size of contaminated areas, concentrations of chemicals of interest in plumes and air, and operating requirements and capabilities of detection equipment.

216. Linking detection information to a UAV's global positioning system (GPS) would allow chemical presence and contamination to be mapped, so that the movement of ground personnel could be controlled to avoid the hazard.

217. Unmanned systems that operate underwater have been developed with automated sample collection, separation and analysis tools (for biological and ecological monitoring). Instruments integrated into the systems are tools and techniques derived from the biomedical diagnostics and research industries, with inspiration from planetary exploration systems (for example the Mars Rover programme). Much development has been seen in oceanographic applications, where new analytical techniques are coupled with traditional sensors to characterise physical, chemical and optical properties of ocean waters alongside real-time biomolecular analysis. Such systems can collected and analyse samples, as well as provide underwater

surveillance. Of relevance to the Convention is the utility of these systems for identifying underwater dumped chemical weapons and associated contamination.

218. Ecological applications for unmanned marine systems include the analysis of environmental DNA (eDNA: DNA expelled from organisms into the environment). This allows retrospective analysis of the types of organisms (recognised by specific markers in the DNA sequence) that may have recently been present in the specific location the sample was taken from. Analysis of eDNA in soil or air samples is also possible. eDNA might serve to recognise the prior presence of a toxin-producing species in investigations involving biological toxins.

219. Needs for tools that aid improvised explosive device and ordinance disposal have led to fieldable and highly capable ground-based robotic systems. Robots can be constructed for specific environments and applications (e.g. for operating in nuclear power plants) and equipped with dedicated auxiliary tools. Repurposing existing robotic platforms lowers barriers to obtaining unmanned ground systems for counter-CBRN applications. Many robotic producers already offer sensors and other devices, which can be integrated into suitable robotic platforms. These modular approaches enable high configurability and interoperability, and customisation with forensic and/or counter-CBRN accessories is also possible. As with any customised robotic system, field testing under relevant conditions is necessary to develop and demonstrate capabilities.

220. Larger robotic systems (specifically land and water systems), while more expensive and less transportable, offer advantages of payload capacity (longer range and operational time due to the ability to carry larger motors and batteries), deployment of more sophisticated of robotic sample collection tools, and the ability to host a variety of detection and analysis tools.

Recommendations

221. Secretariat might consider identifying needs for unmanned systems, developing use cases, exploring scenarios where such systems might be deployed, and training and field testing of available systems that appear to meet needs. Visual imaging, collection of geospatial and temporal information, and real-time chemical detection, make them suited to field use where surveillance can help ensure safety of personnel and inform their decision making. High resolution mapping of investigation sites can be digitally captured (including as a 3D renderings of indoor and outdoor areas), allowing analysis in real time, or later on, and time stamping of the collected images.

222. Retail off-the-shelf UAVs would benefit from evaluation of more suitable sensing and detection capabilities. This might allow the Secretariat and States Parties to find cost-effective solutions for managing chemically-contaminated areas. The Secretariat is encouraged to engage with technology developers to gain access to robotic tools for evaluation.

223. Training and scientific workshops can serve as fora for reviewing new technologies and providing feedback to their developers in relation to operational needs. The Secretariat is encouraged to engage with developers of remote sensing systems to explore the possibility of evaluating commercial systems in training exercises.

OPCW Central Analytical Database (OCAD)

224. The OCAD is a reference library of validated chromatographic, MS and NMR data of chemicals of relevance to the Convention. It enables on-site analysis during OPCW inspections and continues to be regularly updated. It currently contains validated data for over 5,000 scheduled chemicals. It is the largest available library of scheduled chemical data.

225. The SAB was pleased that the Eighty-Sixth Session of the Executive Council took a decision (EC-86/DEC.10, dated 13 October 2017) to include relevant non-scheduled chemicals in the OCAD. The identification of non-scheduled compounds, in particular degradation products and derivatives of scheduled chemicals (SAB-23/WP.2, dated 25 May 2016), RCAs, and CNS-acting chemicals, whose spectra are not in OCAD would be valuable for on-site analysis during OPCW investigations relating to chemical weapons.

226. The SAB recommends including additional chemicals in OCAD to allow the OPCW meet all its mandated inspection aims. This could include salts of scheduled chemicals, toxic industrial chemicals, CNS-acting chemicals, bioregulators, toxins, and unscheduled chemicals that have been identified as posing a risk to the Convention. Isotopically labelled scheduled compounds and stereoisomers of Scheduled chemicals (SAB-23/WP.1), and data for the 60 chemicals considered in the SAB response to the Director-General's request for advice on RCAs (SAB-25/WP.1), would also be useful to include.

Environmental sampling and analysis

227. Environmental sample analysis of matrices such as soil, air, water and vegetation play a key role in the implementation of the Convention. The PT and DL programmes for environmental sample analysis have developed a robust network of off-site laboratories. DL environmental sample analysis capabilities originally developed as anticipated for IAUs and CIs. However, IAUs may require analytical methods different from those used regularly in PTs. The SAB recommends that PTs could be tailored to prepare DLs for scenarios relevant to IAUs and related fact-finding activities, including those that could involve non-scheduled chemicals.

228. Information on environmental chemical signatures, collected via satellite imagery, UAVs, and methods developed for precision agriculture, can assist on- and off-site analysis and guide sample collection. The SAB highlights benefits achievable from the integration of existing and emerging technologies and informatics for automated sample analysis (including drone-based systems), sensor arrays for chemical detection, and real-time environmental imaging and analysis. New technologies enabling the measurement of multiple signals in the environment could be used to detect unexpected chemical change, such as the use of a CWA.

Vegetation an indicator of chemical exposure

229. Verification of compliance and IAUs of chemical weapons require accurate detection of CWAs and their degradation products. Plants can act as a time capsule for retaining the evidence of prior exposure of chemicals in the environment and the Secretariat might benefit from engaging with researchers studying chemical exposure to various plant species. Plants can uptake chemicals from soil and store them, their biomolecules may form adducts with chemicals of interest, and certain chemicals may produce observable and possibly characteristic phenotypic effects (including discoloration and morphological changes). Understanding the molecular basis of such changes may provide opportunities to identify biomarkers to confirm exposure to specific chemicals, including CWAs.

230. A compilation of representative plants and any known and/or potential biomarkers indicative of toxic chemical exposure (particularly to TICs and other relevant unscheduled chemicals) would help the Secretariat and DLs to consider where method development might be valuable. Useful information would include identification of biomarkers and metabolites expressed in response to exposure (independent of whether or not they form adducts or other products incorporating molecular features of the chemical of interest) to CWAs and other toxic chemicals form adducts or other products incorporating their molecular features.

231. Chemical, physical and microbiological changes induced in vegetation upon exposure to toxic chemicals might be exploited during investigations. The SAB, the Secretariat, and DLs would benefit from greater awareness of the capabilities developed in plant science relevant to environmental chemical exposure and should monitor developments in this field.

Analysis of materials

232. Like vegetation, construction materials can retain evidence of chemical exposure. Studies have been published regarding the fate of CWAs in such materials. Chlorine reacts with various metals and can add across double bonds in unsaturated polymeric materials. A compilation of common construction materials and their reactivity towards relevant TICs and unscheduled chemicals could be useful to the Secretariat and DLs for analytical purposes. A compilation of this type might serve as a guide to help select samples for off-site analysis.

International monitoring networks

233. During the scientific review, the SAB has engaged with experts involved in international monitoring networks, notably the Comprehensive Nuclear Test Ban Treaty Organisation (CTBTO) International Monitoring System (IMS) and the Ocean Observations Initiative (OOI). These networks acquire datasets from monitoring stations spanning large areas of the planet and these are available to scientists from member States and/or organisations. They facilitate collaborations between researchers across scientific disciplines and international borders. In addition to enhancing international scientific collaboration, data generated by these monitoring networks have been used to provide early warning of natural disasters, assess

environmental vulnerabilities, and produce inputs for policy-makers to inform land management strategies.

234. Global soil sample collections exist for exploitation by archaeologists and environmental scientists as control samples to compare them against samples collected at dig sites. Such control samples, if available for a location of interest, might have value when analysing samples from sites associated with chemical weapons use.

235. The datasets from these networks and other worldwide monitoring initiatives can include chemical and biological indicators of environmental change with detailed geospatial, temporal and other forms of metadata. World-wide satellite imagery data sets are also available (e.g. Google Earth Engine). In addition to data sets, there also exist sample collections, including for soil that have been collected for exploitation by archaeologists and environmental scientists as control samples. Such control samples (and associated data), if available for a location of interest, might have value when analysing samples from sites associated with chemical weapons use.

236. These data sets and sample collection could assist in the reconstruction of past events. The Secretariat might consider the types of information available and how it might be accessed. Engagement with scientists within international networks would multiply awareness-raising of the OPCW and the Convention.

Legacy chemical weapons

237. Studies have been published monitoring the extent of arsenic contamination from old and abandoned Lewisite munitions. On-site real-time MS monitoring of air samples for arsenicals by Atmospheric Pressure Chemical Ionization (APCI) has been reported.

238. There are estimated to be 130 sites around the world where chemical weapons have been dumped at sea. The depth of the sites determines the accessibility of the munitions and containers. Water temperature and currents influence their rate of degradation, with the CWAs eventually leaking out. Chemical agents such as tabun and phosgene on contact with seawater will hydrolyse quickly. Sulfur mustard is a solid below 15 °C and hydrolysis of solid 'lumps' of this chemical occur very slowly. Sulfur mustard is a problem in shallow waters where it can be retrieved accidentally in fishing nets and may begin to melt under warmer conditions above the surface of the sea. Arsenic from degrading Lewisite can accumulate in oceanic ecosystems. Studies have been published on environmental fate and transport of CWAs and their decomposition products from sea dumped chemical weapons, in particular for those dumped in the Baltic Sea. The SAB notes on-going monitoring of sea dumped chemical weapons can provide useful information related to the environmental fate and transport of CWAs.

<u>Recommendations</u>

239. The environmental fate of chemicals associated with sea dumped munitions is of interest to the CWA analysis community. The SAB encourages researchers collecting

samples from old, abandoned and sea dumped chemical weapons to publish their findings in peer-reviewed scientific literature.

240. The Secretariat could develop a repository of technical information regarding environmental impact of old, abandoned and/or sea dumped chemical weapons, to facilitate knowledge sharing through the Secretariat. This type of information contains useful data for understanding environmental fate and transport of CWAs; which has value for investigative and retrospective analysis.

Biomedical sampling and analysis

Status at the Third Review Conference

241. The OPCW Laboratory had facilitated biomedical sample confidence building exercises with the DLs and proposals for biomedical sample PTs were suggested. The SAB report had noted capability gaps for off-site analysis in IAUs where the analysis of biomedical samples at trace levels may be required. These issues were addressed by the SAB through the TWG on verification and by the work of the OPCW Laboratory.

Status of the field

242. The analysis of biomedical samples to assess exposure to CWAs has been reviewed by the OPCW Laboratory. An edition of the peer-reviewed scientific journal *Analytical and Bioanalytical Chemistry* on "Analysis of Chemicals Relevant to the Chemical Weapons Convention", guest-edited by scientists from the OPCW Laboratory, contains pertinent information.

243. Validated methods for the identification of CWAs in biomedical samples have been developed; however, CWAs have a relatively short lifetime in the body. The chemicals are hydrolysed, metabolised, or form adducts with nucleophilic sites of macromolecules such as proteins and DNA. Their analysis is performed off-site owing to the specialised laboratory equipment and resources required. During the past decade there has been a significant development in methods, these include the use of HRMS for retrospective trace analysis (usually with very low detection limits).

244. Several characteristic CWA metabolites can be found in biomedical samples. The duration from the exposure to sampling determines their probability of discovery. The time frame for detection varies with the severity of poisoning and the limits of detection of the method. It must be borne in mind that some metabolites are not unique to CWAs.

245. Some CWAs react with a specific amino acid of a protein present in the bloodstream (e.g. albumin, haemoglobin, or BuChE) to give adducts. DNA adducts have been reported, mainly with sulfur mustard. These covalent adducts of macromolecules retain some of the structural information of the CWA. Analysis results of samples obtained from a deceased person exposed to sarin in the Syrian Arab Republic have been published, demonstrating the value of the retrospective search for CWA biomarkers in biomedical samples.

246. Other analytical methods are also available to provide evidence of intoxication with organophosphorus nerve agents: fluoride induced reactivation of serine adducts of AChE and BuChE in blood (to regenerate the nerve agent) and identification of the nerve agent adduct of a specific nonapeptide.

247. Biomarker methods have allowed retrospective identification of poisoning by sulfur mustard, nitrogen mustards, Lewisite, organophosphorus nerve agents, the incapacitant BZ, phosgene and hydrogen cyanide.

248. Methods to find a useful biomarker after chlorine exposure are ongoing. Recent work in mice looking at 1-α-phosphatidylglycerol chlorohydrins as potential exposure markers appears promising, but requires further development.

<u>OPCW Biomedical Proficiency Tests (BioPTs)</u>

249. Much progress has been made since the Third Review Conference. Based on experiences gained in the OPCW confidence-building exercises on biomedical samples conducted prior to 2016, written criteria for identification have been stipulated and the OPCW Biomedical PT (BioPT) programme has been instrumental in establishing a system of expert DLs for the analysis of authentic biomedical samples (see S/1516/2017, dated 11 July 2017 for recent status). Samples used in BioPTs have been limited to certified non-infectious human urine and plasma matrices spiked with OP nerve agents, nitrogen mustards, or sulfur mustards, and associated biomarkers.

250. The DL network acts as a deterrent factor to non-compliance to the Convention by adding a high level of confidence to the verification regime. The scientific rigour of these PTs, following the criteria laid down by the International Organisation for Standardization (ISO) 17025 quality system and OPCW quality management system ensures this high level of confidence.

251. During a CI, IAU, or other OPCW investigation, environmental and biomedical samples may be taken. The main biomedical sample types are blood, plasma and urine, but depending on the case, additional samples, such as hair and tissue samples, can be taken. Biomedical samples from victims of exposure can provide strong evidence of the use of CWAs.

<u>Recommendations</u>

252. The number and geographic locations of DLs (for both environmental and biomedical samples) allows flexibility in the selection of which laboratories off-site samples are sent. Yet, it remains desirable to have DLs available from all regional groups. The SAB supports expansion of the DL network and notes that this network serves as a model of international scientific cooperation in support of the Convention. Technical data related to IAUs should be shared among DLs and published in peer reviewed scientific literature to build capacity worldwide that the OPCW may wish to draw upon in future. These publications would consolidate and strengthen through scientific peer review methods for verification of compliance to the Convention. Joint publications from DLs would benefit all DLs by describing proven methods and technologies that can be adopted by all.

253. The OPCW and its DLs for environmental and biomedical samples have attained a high technical competence in identifying scheduled chemicals and their degradation products. Analytical instruments and methods continue to evolve and improve Convention-related analysis. Further work on the storage of samples just after sampling and during transport to the OPCW Laboratory, sample handling during splitting, and storage and disposal of samples at the OPCW Laboratory should be pursued. To minimise degradation of chemicals in the samples, as little time as possible should elapse from the time of collection of the samples to the time of analysis. International collaboration with expert laboratories working in the field of Convention-related analysis to maintain updated Recommended Operating Procedures (ROPs) is important. These methods provide guidelines for DLs or laboratories applying for designation.

254. In regard to enhancing the capabilities available to the OPCW Laboratory and the DL network, the SAB strongly supports the efforts to upgrade the OPCW Laboratory to a Center of Chemistry and Technology (see S/1512/2017, dated 10 July 2017; and S/1561/2017, dated 8 December 2017). Following many of the recommendations in this report would provide augmented capabilities to the upgraded laboratory. The SAB believes that the value of the DL network would be maximised with additional laboratories completing technical agreements to accept real samples, to widen the set of DLs capable of performing off-site analysis for OPCW contingency operations.

255. Availability of reference materials is critical to avoid misinterpretation. Reference samples are needed to support unambiguous identifications; however, not all target chemicals can be reproduced with spiking. The inclusion of analytical data of biomarkers into the OCAD is suggested. This data could enhance the analysis capability during on-site investigations.

256. Current OPCW biomedical PTs do not address the identification of intoxication from non-scheduled or novel toxic chemicals. This may, for example, be important for an IAU or Fact-Finding Mission, when there is evidence that a toxic chemical has been used for prohibited purposes, but no scheduled chemical can be found. As shown by the recent use of chlorine as a chemical weapon, the development of analytical methods for detecting exposure to toxic chemicals of relevance to the Convention from biological samples would strongly support the investigation. At present, only a few methods for retrospective identification of poisoning by chlorine have been reported. It is important to develop capabilities for the sampling and analysis of authentic environmental and biomedical samples from incidents involving TICs and other unscheduled toxic chemicals of relevance to the Convention. Subsequently, ROPs could be developed. The SAB recommends that the Secretariat, with the support of DLs and other relevant experts, evaluates a possible approach for adopting methods that can be used for TICs.

257. The SAB supports the Secretariat's efforts to establish capabilities for the verification of the Schedule 1 toxins saxitoxin and ricin. Development of analysis of specific biomarkers of these toxins from biomedical samples would also be advantageous; e.g. q-NMR could play an important role in identifying and quantifying the toxins. Such an approach has recently seen success in pharmaceutical research and for the

identification and quantification of marine biotoxins in samples containing mixtures of compounds.

258. Bringing together experts from a broad range of fields to share experiences could strengthen the development of new methods for collecting and analysing biomedical samples relevant to the Convention. In regard to unscheduled chemicals and the wide range of chemical compounds (and especially TICs) that could potentially be used as chemical weapons, the SAB notes that forensic toxicologists are often faced with identifying chemicals responsible for fatalities without knowledge of what they need to look for. Experiences in the forensic toxicology field may be informative for further developing biomedical sample capabilities of the Secretariat and the DLs.

259. Recent advances in breath analysis could provide new approaches for investigations of poisoning by CWAs or other toxic chemicals. Breath analysis is suited for diagnosis of cancer, infectious diseases, food intolerances, and diabetes. The presence of specific markers for CWAs or toxic chemicals in a breath fingerprint would constitute evidence of intoxication. Developments in this area should be monitored for their practicability for determining exposure to chemicals.

260. High-throughput OMICS technologies (e.g. genomics-transcriptomics-proteomics) can be combined for defining biomarkers for diagnostic purposes. The field of proteogenomics is aimed at integrating large-scale data for improving genome annotation and identifying specific molecular targets that could define a given biological phenomenon. In addition to better characterisation of biological systems, these approaches may be used for detecting and quantifying organisms without any prior information.

261. Advances in the analysis of biomedical samples occur in parallel with those in medical diagnosis and MedCMs Studies of the metabolism of toxic chemicals in marine organisms near sea-dumped CWAs may provide insight into non-human biomedical sampling. The analytical methods might be transferable to the detection and identification of CWAs in casualties of chemical weapons.

Sample storage and stability

262. In the context of OPCW investigations, including Fact-Finding Missions and the Declarations Assessment Team, the Secretariat has since 2013 received numerous samples, which are stored in the OPCW Laboratory at room temperature or refrigerated at 4 °C. The SAB considered best practices for sample storage and the impact of sample stability on analytical results (SAB-23/WP.2, dated 25 May 2016).

263. The SAB recommends as best-practice conditions for long-term storage of biomedical samples, to ensure their integrity for up to several years, to store them in polypropylene or polyethylene terephthalate containers in a freezer at -80 °C (except for whole blood which should be refrigerated at 4°C). Blood cells and plasma should be separated from the blood samples as soon as possible, as storing whole blood in a freezer leads to cell breakage.

264. The SAB notes that stored samples will naturally degrade, and the best choice of storage conditions may only slow down the process, leading to loss of the intact

original chemicals by degradation, in, at worst, weeks to months, and at best, months to years. The main degradation of CWAs or other Convention-relevant chemicals in environmental samples occurs through hydrolysis and/or oxidation The SAB assesses that it is difficult, given the incomplete knowledge worldwide of the fate of CWAs and other Convention-relevant chemicals in different matrices, to specify precisely when analysis of a sample can no longer identify the intact original chemicals. The best-practice storage conditions recommended by the SAB will extend the time the original chemical remains intact in the sample. Some loss of this chemical may occur even under these conditions but the analysis of the samples will return credible analytical results though 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 for proving CWA production, chemical weapons use or other Convention-related compliance judgement.

265. Sample types containing chemicals of interest, such as various nerve and blister agents, as well as their immediate precursors and degradation products, may include, for example:

(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 either relatively high levels or trace levels of the chemicals of interest; and

(d) Biomedical samples: blood, plasma, urine, tissue.

266. 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 not diminish their usefulness as evidence in IAUs or other Convention-related investigations. Two recommendations were made to address this concern:

(a) Samples should be analysed as soon as possible after collection to eliminate the need for storage or at least the storage time minimised.

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

<u>Sample preparation</u>

267. For sample preparation for chemicals relevant to the Convention, the Blue Book, a collection of the ROPs for Sampling and Analysis in the Verification of Chemical

Disarmament, was updated in 2017 by VERIFIN. These methods provide the guidelines required by DLs and any laboratories applying for designation.

268. Allegations of the use of chlorine as a chemical weapon have highlighted the need to expand the sample preparation capabilities to non-scheduled chemicals. Further work on development of sample preparation methodologies for relevant non-scheduled chemicals (including TICs, RCAs and CNS-acting chemicals) should be pursued.

Forensic and investigative science and technology

Overview

269. The lessons learned from contingency operations, such as the OPCW Fact-Finding Mission in the Syrian Arab Republic, have highlighted the need for evaluation of technologies and adoption of methods (both current and emerging) applicable 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 events.

270. There are many places where enabling technologies might provide value to inspectors for missions with investigative mandates. However the adoption of any new technology must consider the operational requirements and practical issues that might arise in the field. Limitations and challenges need to be considered, together with sample, analytical and data integrity (including chain of custody) throughout the investigative process. For field tools, limitations can include power sources required for use, availability of consumables, set up time, and transportation requirements (including shipping weight and possible shipment restrictions). Further complicating the use of data driven technologies are potential restrictions on data transmission and the need for accurate and precise record keeping with regard to chain of custody.

271. To consider practical applications of investigative methods and technologies and where they could enhance capabilities, the Director-General requested the SAB to establish a TWG on investigative science and technology. This TWG is undertaking an in-depth review of methods and technologies that could be used by OPCW inspectors for investigative work. This review will include relevant considerations from the SABs scientific review. The TWG has a two-year term of reference and the report of its first meeting has been published (SAB-27/WP.1, dated 26 February 2018).

Capabilities of forensic methods

272. In addition to the sampling and analysis techniques used in recent OPCW contingency field operations, augmentation with other forensic investigative techniques employed by international organisations involved in investigative work and national law enforcement might be valuable for OPCW field operations. Examples include forensic analysis of open-source videos and documents to establish their authenticity, and forensic accounting of materials and funds. The TWG should identify commonly used forensic techniques and assess their applicability and value for the OPCW.

273. Traditional forensic techniques, including DNA analysis, fingerprinting, chemical criminalistics, quality management and crime scene management capabilities, may be valuable for OPCW field operations. Consideration should be given to the establishment of a forensic management team to support the OPCW ahead of mission deployment and to provide oversight of forensic operations before, during and after a mission.

274. Interagency cooperation, particularly in the development and oversight of forensic capability, would provide capability advances for the OPCW.

<u>Recommendations for scene management and sample integrity</u>

275. Chemical forensics and evidence management is a critical capability to develop. The Secretariat might consider compiling best practices with key stakeholders.

276. The Secretariat would benefit from reviewing recommended best practices for responders who detect, document and take samples in contaminated environments, with a view towards establishing internationally validated training materials on best practices.

277. The utility of autonomous and remote systems for assessing and documenting investigation sites should be evaluated in the context of contingency operations, IAU and the rapid response and assistance mission (RRAM) operations. This would enhance accessibility to otherwise dangerous or difficult to reach areas. Satellite imagery would complement and potentially strengthen the documentation.

278. The utility of UAVs (and any linked GPS information) in support of investigations should be further explored, with specific emphasis on area reconnaissance, scene documentation, live entry support and basic detection. UAV imaging capabilities could also be used to verify and record chain of custody.

<u>Data collection and management</u>

279. Reviewing advances in analysis tools for cross-referencing, validating, and linking information related to investigation sites, materials collected/analysed and individuals interviewed, would inform the development of a system to better support the collection and management of data by the OPCW. Information management systems should integrate disparate sources of data and provide secure and readily searchable capability. To expand forensic capabilities a comprehensive systems-based approach where the separate elements of information are combined and analysed systematically is needed.

280. The SAB recognises the need for a database for forensic purposes that could include existing analytical data, designs of abandoned chemical weapons, and impurity profiles for synthetic routes to CWAs.

281. The effective and sensitive collection of data from victims, witnesses and responders from different cultural backgrounds requires specialist training and advice that considers psychological and sociological aspects. Consideration should be given to providing training and oversight of this type of data collection.

Sampling, detection and analysis

282. Autonomous systems can be used to support inspectors during contingency operations or IAUs, or by the RRAM. These systems (both existing and in development) can be utilised to guide evidence collection, determine sampling hot-spots, support in-situ sampling and on-site analysis, and in detection systems.

283. Reference samples should be kept in the OPCW Laboratory to allow chemical forensic comparison to samples suspected of containing Convention-relevant chemicals if need arises. These samples could also be used for capability development purposes when they are no longer needed to support an investigation.

284. As technology develops, instruments are becoming smaller, more portable, and in the case of some biosensors, disposable. Given the value of miniaturised detection devices for field work, including reduced logistic burden, developments in this area could enhance data collection capabilities that support investigations.

285. Analytical procedures and protocols should be reviewed to ensure flexibility to handle different sample types, large sample numbers, and to accommodate short time-frames whilst ensuring robust analysis and reporting. Lessons learned from contingency operations in the Syrian Arab Republic have been important in shaping the analytical requirements for any future contingency operations and IAUs.

286. Environmental monitoring could find use in contingency operations and IAUs. Satellite imagery allows visual inspection of areas where an incident could have taken place; hyperspectral, thermal and/or infrared images might identify features (especially in vegetation) indicative of the event.

Recommendations for provenance

287. Analysis methods for provenancing and attribution are well-developed fields in forensics. Methods using impurity profiling and isotopic ratio distribution for purposes related to determining the responsibility for use of chemical weapons, for abandoned chemical weapons, or for clandestine chemical weapons production, are valuable to develop. The possible profiling of impurities not related to the product, such as solvents, trace metals and inorganic elements, should be considered.

288. Collection and curation of samples, analytical information and annotation that may not be immediately actionable is advisable. A searchable collection of physical objects and information is valuable for retrospective review. For example, existing compiled data on abandoned chemical weapons and impurity profiles for known synthetic routes to CWAs could aid chemical weapons-related investigations.

DESTRUCTION OF CHEMICAL WEAPONS

289. The SAB stated in its 2008 science and technology report that the technologies and processes for the destruction of declared chemical weapons stockpiles had matured. The corresponding SAB report in 2013 allowed this assessment to stand; by that point both the United States of America and the Russian Federation had adopted the technologies to be used in completing the destruction of their declared chemical

weapons. In 2018, the 2008 judgment remains valid. The United States also employ bioremediation systems for treating the effluents of CWA hydrolysis, where bacteria metabolise the organic CWA breakdown products, converting them into harmless products.

290. Since 2013, the destruction of the declared Syrian chemical weapons stockpile and the remainder of the declared Libyan chemical weapons stockpile have involved well-known technology. The innovation has been in the removal of chemical weapons for destruction outside the territory of the declaring State Party, either on a ship (using field deployable hydrolysis systems) or in a commercial chemical disposal facility located in another State Party.

291. Catalytic materials based on metal-organic frameworks (MOFs) have been developed that can increase the rate at which CWA hydrolysis occurs (demonstrated on nerve agent and sulfur mustards). Such materials have potential use in portable hydrolysis systems to reduce the time required for the hydrolysis process to reach completion.

292. Plasma arc waste destruction systems have also been proposed for use as portable toxic chemical destruction systems; such units are often used on ships for waste disposal. The SAB is aware of research efforts to demonstrate applicability to CWA destruction but is not aware of the use of this method in declared stockpile destruction activity.

293. Destruction technologies for non-stockpile munitions, whether abandoned chemical weapons or old chemical weapons, have remained relatively static over the last five years and seem likely to remain so in the near future. The SAB should continue to keep a watching brief on the development of new destruction technologies and inform Member States of significant developments, especially in the area of mobile destruction systems.

ASSISTANCE AND PROTECTION

Physical Protection

294. The SAB has reviewed available personnel protective equipment (PPE). While many reports of nanotechnologies and other means of potentially enhancing PPE exist (as described earlier), there have been no significant advances in PPE since the Third Review Conference.

Chemical detection

295. The more technical aspects and developments in chemical detection are discussed in other sections of this report. The SAB has surveyed commercial point detectors, chemical identifiers, standoff-detectors, fixed site detectors and open path sensors, and has concluded that:

(a) There have been no major technology breakthroughs in the available chemical detection tools that often accompany PPE. Field detection is generally presumptive, with tools designed to determine the presence of chemical hazards (CWAs or TICs) to support tactical decision-making. This can involve an automatic warning of a chemical release using fixed site, stand-off and/or open-source detectors, or manual detection and classification of liquids or vapours using point detectors. Chemical identifier technologies are available to provide field determination of an identified chemical hazard to support decision-making.

(b) There are gaps and limitations associated with the technologies described. These include poor detection of impure CWAs and low concentrations of CWAs (such as at the health effect threshold); limited ability to detect aerosolised chemicals; limited detection range (which impacts early warning); and limited capabilities to detect non-traditional and low volatility chemical agents.

296. In reviewing and evaluating available field detection equipment, technologies capable of operating at standoff-ranges to provide warning of vaporised and aerosolised chemicals; technologies that allow non-intrusive, non-contact detection and identification of chemical agents in munitions, tanks, or storage vessels; detection technologies with sufficient sensitivity to confirm efficiency of decontamination processes on PPE; and technologies that can improve surface contamination monitoring, should all be considered.

Medical countermeasures (MedCMs)

297. Effort continues to be directed towards the development of improved MedCMs against CWAs, although translation into therapeutic drugs has been slow. A new drug would have to undergo rigorous testing, which would include preclinical and clinical studies, before it could be licensed.

298. There has never been a greater need to find fast and efficient means to diagnose and treat people who have been exposed to toxic chemicals. Research into more effective methods continues and many gaps still exist. Developments across the fields should be regularly monitored and efforts made to bring experts working in civilian and government organisations together to share best practices.

299. Treatment of exposure to toxic chemicals requires MedCMs and decontamination procedures (for the victims of exposure, surrounding infrastructure, and their immediate environment). Appropriate consideration must be given to both aspects when evaluating procedures for response to chemical incidents.

Nerve agents

300. The current medical treatment for nerve agent poisoning employs atropine or another anticholinergic drug, an oxime to reactivate the inhibited AChE, and an anticonvulsant drug, such as diazepam, to minimise neuropathological damage to the brain. Some armed forces use pre-treatment with the reversible cholinesterase inhibitor pyridostigmine to improve protection, particularly against soman.

301. The search continues for an effective broad spectrum oxime reactivator of nerve-agent inhibited cholinesterase. Each of the fielded oximes has limitations, as illustrated by the range of different oximes that are included in military medical kits (e.g.

pralidoxime (2-PAM), trimedoxime (TMB-4), methoxime (MMB-4), obidoxime (LüH-6), and HI-6).

302. An alternative approach to pre-treatment and immediate therapy for nerve agent poisoning is the use of a scavenger to detoxify the nerve agent before it reaches its biochemical target. Human plasma-derived and recombinant human BuChE have been investigated as candidates for a number of years. Effectiveness has been demonstrated in experimental animals, but there are problems relating to the supply and pharmaceutical use of BuChE. A disadvantage to BuChE as a scavenger is that it forms a stoichiometric 1:1 adduct with the nerve agent which, like inhibited AChE, is irreversible in the short term, thus requiring a relatively large mass of the proteinaceous enzyme to be administered. Attempts are in progress to find or engineer an acceptable catalytic scavenger. Enzymes that hydrolyse nerve agents (phosphatases) are also being explored, including the application of synthetic biology to engineer improvements over the naturally occurring enzymes.

Vesicants

303. The toxicity mechanisms of vesicants (blister agents) need to be thoroughly understood and there is ongoing research to this end. The need to defeat gas masks which reduced the effects of suffocating gasses initially used in World War I led to the development of vesicant CWAs. The “lead” agent in this class, sulfur mustard, was first used in 1917, producing large numbers of casualties that did not die from exposure, and which required prolonged nursing care. In the years since 1917 a number of other vesicants were identified and developed as toxic agents, including the nitrogen mustards, Lewisite and phosgene oxime. Sulfur mustard remains the most common vesicant and since its first use as a CWA, it has been used for little else other than to wage war. It has also been the subject of a large amount of research to define its mechanism of action and though much has been studied and published, the precise biochemical event that initiates injury remains elusive. Sulfur mustard is a bifunctional alkylating agent, sharing this property with the nitrogen mustards. Lewisite contains an arsenic atom that is linked to its activity as a vesicant. The interactions of the vesicants have been well characterised and the mustards alkylate key tissue components (DNA, proteins, lipids etc.). Similarly, the arsenic atom in Lewisite combines with thiol groups, inhibiting several key enzymes.

304. Reducing sulfur mustard toxicity remains the most effective way to avoid long-term toxic consequences.

305. There is a continuing need to identify early biochemical events to understand better the mechanisms that lead to vesicant injury. OMICS technologies and in vitro assays can help in this regard. Cell lines that show resistance to sulfur mustard have also been developed to probe the biochemical mechanism of action of sulfur mustard.

Long-term health effects of exposures to nerve agents and vesicants

306. The delayed toxic effects that can manifest upon acute and chronic exposure to sulfur mustard and nerve agents are important to understand for post-exposure treatment. The clinical signs and symptoms of delayed effects are very diverse, resulting in difficulty for physicians to diagnose and differentiate their pathogenesis.

307. Long-term complications reported in survivors of sulfur mustard exposure include: respiratory, reproductive, ocular, dermatological, hematologic, neurological, immunological, psychological complications and cancers. Alkylation of DNA by sulfur mustard can induce long-term complications including genotoxic and reproductive effects. The most concerning delayed effect is the induction of cancer through both genetic and epigenetic mechanisms. Treatment of sulfur mustard associated malignancies by the use of novel gene therapeutics, cancer vaccines, and epigenetic medications have been studied.

308. In the case of nerve agents, reported long-term effects include neurological, hematologic, cutaneous, cardiovascular and psychological complications; as well as pulmonary diseases and lung damage. More research is necessary to clarify adequately the molecular mechanisms of such long-term effects, and to provide useful advice to physicians and health professionals to improve healing. Some information on delayed effects of these toxicants and medical management of their long-term health effects has been published, particularly after the nerve agent attacks in Japan during the 1990s. Some of the delayed effects can be managed by readily available medicines.

309. Gene therapy might also be a future direction for treating nerve-agent poisoning, offering the possibility of transitory production of scavengers or degrading enzymes in the body. However, safe and effective gene therapy is currently a long way off clinical use.

Recommendations

310. Sulfur mustard exposure can induce long term health complications. Treatment of these long-term adverse effects is one of the most pervasive healthcare issues faced by the survivors, with cancer being one of the most serious consequences.

311. Much information exists on how to respond to chemical incidents. However, there is little international standardisation (even to the point that some responders are not allowed to deploy MedCMs that are stockpiled by others for use in emergencies). The procedures are in many cases specifically tailored to certain groups (e.g. for military personnel, emergency responders, etc.) and for a general civilian population may not represent best practice (for children, the elderly etc.). A compilation of information categorised according to whom it could apply to would be useful.

312. The SAB notes that there have been suggestions for the use of gene therapy for the treatment of the long-term effects of sulfur mustard injury. Advances in gene-based therapeutic approaches for treatment of disease and injury and their potential applications to CWA-induced injuries should be monitored.

313. Emerging technologies relevant to MedCM development include organ-on-chip devices that allow screening of the toxic effects of chemicals. Organ-on-chip devices are collections of cell structures that mimic the cellular composition of organs, sufficient that the likely physiological response(s) of the organs can be studied. Computational methods developed to predict toxicity and toxicological response of certain chemicals also exist. These may be useful for identifying targets for drug

development and in the early stages of gathering data for meeting any regulatory requirements.

314. There has been considerable progress in the development of vaccines for toxins (including ricin and botulinum) and for CNS-acting chemicals, such as opioids and fentanyls. Progress of research on these vaccines should be followed.

Decontamination

315. Decontamination is the process of removing and preferably neutralising toxic chemical agents. Current methods can be separated into two categories, as follows:

(a) Physical decontamination: this encompasses all passive methods without chemical reaction, aimed at removing the chemical from any given surface. It relies on mechanical action to absorb, remove, or flush the agent away, but does not destroy it.

(b) Chemical decontamination: this refers to methods that detoxify the toxic chemical through chemical reactions. Destruction of CWAs can involve hydrolysis, elimination and/or oxidation reactions, including through enzymatic processes. Developing decontaminants requires consideration of the range of temperatures of potential use, and rates of the processes used to neutralise the CWAs, forming non-toxic products. The most effective decontaminants readily solubilise CWAs.

316. An ideal decontamination device would include a delivery system that readily cleans surfaces and whose decontaminant spray causes rapid and efficient neutralisation and/or destruction of the toxic chemical, maximising the speed of decontamination and reducing health and environmental impact. Improving chemical knowledge of the detoxification reactions, characterisation of the products formed, and the potential toxicity of these compounds, remains challenging. Consideration of the effects of the decontaminant itself on materials, and on the environment and human health, is necessary.

317. Research in the field continues and examples of rapid degradation have been reported; new developments include the use of nanoparticles, enzymes, photochemical and catalytic approaches, and MOFs. Furthermore, considerable efforts have focused on reducing water consumption for decontamination, with dry systems demonstrated. Integration of the decontaminant agents into textiles for protective clothing is another area where developments should continue to be monitored.

318. Although decontaminants are designed for general detoxification purposes, it is very difficult to find a single effective decontaminant against all classes of CWAs, and some are effective only for specific agents. A universal decontaminant that can detoxify both chemical and biological agents remains a long term goal.

319. Decontamination systems suitable for civilian emergency response are becoming available; the suitability of these for OPCW activities should be assessed.

SCIENCE AND TECHNOLOGY FOR CHEMICAL SAFETY AND SECURITY

320. The past two decades have seen an increasing use of explosives to cause harm. There is widespread knowledge of the construction of improvised chemical dispersal devices and facile access to commercial chemicals. The increasing accessibility of chemicals has increased the risk of chemical terrorism and intentional misuse of chemicals. While regulatory systems and import and export controls can restrict access to chemicals, diversion, use, and abuse of chemicals continues to present a safety and security risk. Furthermore, improvised delivery methods will be a continual challenge as it may be difficult to regulate the components that might be used (for example, electronic components, including those in teaching-focused science kits, and/or household items such as pressure cookers). Addressing these risks provides a number of opportunities for science and technology based approaches that could help to reduce the accessibility to chemicals and the capability to misuse them, as well as to recognise the presence of hazardous chemicals before they may be dispersed.

321. New technologies that may have a chemical safety application include the Internet of Things (IoT). This is exemplified by the smartLAB project, which uses the IoT to create an intelligent, web-connected system that can gather data from laboratory devices, analyse them, and provide laboratory workers with quick, reliable and best practice solutions, as well as the potential to trigger devices to take an action. Devices being developed include self-cleaning "smart" lab benches, and smart safety goggles which can display and project safety information. Advanced chemical inventory software is also being used to increase safety awareness and alert laboratory staff to hazards, proper handling and storage, and precautions necessary to work with a given chemical (in effect this provides instant access to material data safety sheets).

322. The IoT and software tools being developed could help overcome some current challenges that arise from unenforced chemical safety legislation, improperly labelled hazardous materials, communication and language issues arising as chemicals are internationally transferred, and mapping of hazardous chemicals within a local area. Real-time access to data on chemicals of high risk of misuse would benefit regulators and responders alike; many agencies and organisations have developed databases, and there is a wealth of available scientific databases with complementary information, that could usefully be accessed.

323. Computational tools that can model chemical accidents (spills and/or gas releases and dispersion) are seeing increasing use to aid the preparation for accidents involving hazardous chemicals. Virtual reality simulations have also been developed for accident and response training. Computational tools such as those described can also aid in risk assessment. Chemical supply chain risk mitigation (CSCRM) modelling tools are available that can provide guidance for minimising risks associated with chemical transportation, assessing management decisions under various safety related scenarios, and developing strategies to improve chemical security. Overcoming the often encountered challenges of a lack of knowledge and adherence to chemical safety rules could be achieved through integrating layers of chemical safety within specialist software used in chemical commerce and making these tools more broadly accessible wherever possible.

324. In regard to chemical security and contributing to efforts to mitigate chemical threats from non-State actors, the SAB recognises that the Secretariat has initiated activities (for example, EC-87/DG.17, dated 23 February 2018). There are a number of guidelines and documents providing information on best practices and the development of anti-terrorism standards available, and like the Convention itself, many of these documents have been developed with scientific and technological inputs. The SAB recognises these are critical inputs to consider. The SAB encourages the Secretariat to engage with technical experts to ensure there is a sound scientific basis for its inputs into chemical security issues.

325. Scientific communities have also contributed to chemical security through scientific research projects aimed at making certain chemicals useless when diverted from their original purpose. Examples include additives that can prevent a chemical from being concentrated for use as a precursor for synthesis of explosives (in particular hydrogen peroxide), bimetallic alloys that promote degradation of explosive contaminants in water, ambient intelligence and communication technologies for monitoring dangerous chemicals, and improved tools for real-time and on-site analysis of chemicals that could pose a risk to the object and purpose of the Convention (many of which have been highlighted previously in this report).

326. In relation to on-site chemical detection capabilities for security applications, IMS has seen widespread implementation (for identification of chemical explosives or CWAs); however, this technology can suffer from drawbacks such as a low resolution. DART-MS enables detection of chemicals of low volatility. Other technologies that can identify hazardous chemicals from surfaces include laser desorption techniques such as MALDI, laser desorption/ionization (LDI), ambient pressure laser desorption (APLD), ambient pressure-laser induced acoustic desorption (AP-LIAD) and surface-assisted laser desorption/ionization (SALDI).

Recommendations

327. Technologies which can help detect, predict and/or prevent risks associated with the use of hazardous chemicals as well as aid in ensuring readiness to confront various chemical incidents can be useful for chemical safety and security purposes. Applications of computational tools, real-time data analytics, on-site detection methods, and technical solutions for reduction of capability to misuse certain chemicals and their precursors have been demonstrated.

328. The SAB encourages the Secretariat to consider innovative ways to use science and technology in its activities in chemical safety and security, and its contributions to countering non-State actor use of chemical weapons. Identifying available tools and facilitating access (especially to chemical information) could be beneficial for those implementing chemical security measures. The Article XI programmes of the Secretariat, such as the research support programme, could be a means to encourage research and development with chemical security relevance, perhaps in conjunction with the upgraded OPCW Laboratory and its international partners. End of project meetings of funded researchers could provide a forum for discussion and exchange of ideas that would provide insights into how to best evaluate and use technological solutions, and how to make these solutions broadly accessible.

329. The SAB has been informed that a number of States Parties, whose economies are either developing or in transition, have expressed interest in improving their chemical safety and security capabilities, specifically in monitoring the transfer of chemicals into and out of their territories. The SAB recommends the Secretariat strengthens its partnerships with international organisations engaged in research and development of technologies for this purpose. Further, the SAB recommends the Secretariat pursues collaborative projects with such organisations to develop additional internal expertise to assist States Parties.

SCIENTIFIC LITERACY AND SCIENCE ADVICE

330. Understanding developments in science and technology is essential for the full and effective implementation of the Convention, as scientific and technological underpinnings are found throughout its Articles. In fulfilling its mandate to render specialised advice to the Director-General, the SAB has attached importance to staying abreast of developments in the OPCW's work to comprehend the context in which scientific insight is sought on specific issues. At its regular sessions the SAB has been briefed by members of the Secretariat and invites external experts to make presentations on innovative research relevant to the OPCW's work. The SAB has prepared responses to requests for advice on specific issues and has established TWGs to prepare reports on broad areas, such as convergence, verification, and education and outreach (E&O), in which extensive discussions involving outside experts was necessary.

331. The insight brought into discussions by members of the Secretariat, especially inspectors and the OPCW Laboratory regarding fieldable and operational needs and challenges, is an essential aspect of recognising opportunities where a given technology might prove valuable. The practice of engaging operational staff from the Secretariat in the scientific review process has aided the formulation of practical science advice, and allowed the SAB to provide scientific guidance on operational practices. The Secretariat is encouraged to maintain this discourse with the SAB.

332. The SAB has sought to broaden the participation of outside experts beyond the regular sessions of the Board in the lead up to the Fourth Review Conference for identifying important developments in science and technology. This was enabled by generous funding from the European Union that allowed the SAB's international workshops on chemical forensics, MedCMs and emergency response, innovative technologies, and chemical production, to be held. These workshops had a combined attendance of more than 180 participants from 40 States Parties, included 111 presentations and briefings, and provided extensive material for the current report to the Fourth Review Conference on scientific and technological developments.

333. The SAB recognises the value of drawing on the experience of other international organisations in obtaining and making use of advice on scientific and technological developments relevant to its own work. The SAB has established informal links with other science advisory mechanisms and scientific societies with policy and science advice interests to share best practices and provide valuable insights; such links should be expanded and the SAB recommends seeking further opportunities to engage with scientific advisory boards of other relevant international organisations. The SAB

has placed great importance on its practice of holding workshops and producing reports in support of the scientific review to the Fourth Review Conference in cooperation with partners such as the International Union of Pure and Applied Chemistry (IUPAC).

334. Recognising the importance of informing delegations more fully on its work and getting their feedback, the Secretariat facilitates SAB Chairperson and Vice-Chairperson briefings to States Parties and in 2014 initiated "Science for Diplomats"[21] as an interactive briefing to be held on the margins of Sessions of the Executive Council and Conference of the States Parties to engage delegations on the findings of the SAB. These regular interactive briefings have been valuable for strengthening scientific literacy and ensuring technical dimensions are adequately considered and understood by the Convention's policy-making organs.

335. As an independent advisory body on scientific matters, the SAB notes that Convention-relevant decision makers should have access to, and carefully consider, the scientific insights needed for their deliberations. Advice and informative views on how science and technology are changing the world may challenge assumptions and spark innovative ideas to take forward. The SAB recognises that science and technology represent one of many dimensions to policy decisions and recommendations based on purely technical considerations may not always be translated into policy. However consideration and discussion of the scientific advice by the decision makers strengthens the quality and impact of their decisions going forward.

336. The experiences developed by the OPCW SAB have revealed a number of aspects useful for the provision of science advice in international forums. The work of the SAB has been enabled through consideration of:

(a) technical dimensions with an independent and objective perspective;

(b) evidence based assessments that consider all relevant information (including insights into the driving forces of technology development);

(c) a formalised feedback mechanism (e.g. Director-General responses to SAB reports through official documents of the OPCW);

(d) continual engagement and interactive science communication with stakeholders;

(e) the science policy adviser position at OPCW; and

(f) funding to organise and support meetings and briefings (through the SAB trust fund and beneficial financial support from the European Union).

21 For further information on Science for Diplomats see: www.opcw.org/special-sections/science-technology/science-for-diplomats/.

337. The SAB recognises that any scientific advisory mechanism must be suited to the recipients of the advice for it to be effective. This necessitates that the advisory mechanism takes into account the purpose of the advice, and how it will be received and acted upon by its recipients.

338. The SAB plans to continue the established process for providing advice, which has demonstrated its value, but also to improve the ways it gathers information and communicates its findings: to ensure that all relevant information is considered and that the results of its discussions can be taken into account fully by policy makers. The SAB views sharing of experiences of providing science advice with stakeholders of other relevant disarmament communities as a valuable contribution to the strengthening of scientific literacy for non-proliferation.

339. Given the wide fields of science that continue to advance, and contemplation of where to take action, the SAB encourages policymakers to consider their needs and identify gaps and priority areas that require the technical dimensions to be evaluated and converted into scientific advice. The transdisciplinary nature of scientific advancement requires approaches to addressing technical issues that look to capability rather than scientific developments that fall under specific (and often artificial) disciplinary labels.

Horizon scanning and technology foresight

340. As science continues to advance and drive technological evolution, the technological landscape will be one of continual change. In such a dynamic technological landscape, identifying trends in science and technology and predicating their ultimate trajectories and impact will remain a challenge. Within the five year period, between the Third and Fourth Review Conferences, a number of trends and concerns in technology development have experienced shifts in focus, as expectations of technology advancement in some sectors have fallen short while others have witnessed unexpected jumps in capability. Recent advances in gene-editing technologies, AI, and UAVs have been significant, despite the fact that such capabilities, albeit in less advanced forms, have existed for decades.

341. Horizon scanning and technology foresight tools and capabilities play a significant role in recognising and harnessing technological change to prepare for future challenges to the implementation of the Convention. Developing suitable methods and maintaining access to relevant experts to provide insights must therefore be a priority for the scientific review process and for the OPCW in general.

342. Scientific information is readily accessible through scientific literature (in particular peer-reviewed journal articles and patents), scientific news, reports of funding agencies and government science ministries, conference reports and scientific social media. Many techniques and methods have been developed to identify trends, drivers of change, "weak signals", disruptive and/or "game-changing" technologies, interfacial research, uncertainties, and discontinuities of technological developments. In the view of the SAB, keeping a watching brief through desk searching and informatics tools alone is not adequate to fully understand and identify relevant developments. This is further complicated by terminology and classifications of areas

of scientific development that might help to identify specific scientific communities, but may not convey similarity or identical capabilities emerging from a diversity of fields of research. Engagement with expert communities (including academia, industry, and government) remains a critical aspect of the review process. The SAB encourages participation of the OPCW science policy adviser and its members in scientific conferences and continued engagement with relevant scientific networks. The SAB notes that effective horizon scanning requires collaboration among information specialists and a broad range of subject matter experts.

343. The complexity of issues relevant to the Convention, combined with evolving and dynamic security concerns, presents challenges for reliably predictive horizon scanning and technology foresight. Issues include identification of relevant (and geographically distributed) experts; obtaining holistic perspectives on trends, applications and fieldable capabilities; and recognising where technological developments from a diversity of sectors with unique operational requirements can be used to solve technical problems related to effective implementation of the Convention. The SAB suggests that if interactive forecasting approaches (the Delphi method for example) are considered, the aforementioned factors should be considered in the design of the study. Understanding the findings and outcomes of ongoing security-related science and technology foresight would be valuable for providing inputs to the scientific review process. Horizon scanning and technology foresight researchers could be invited to brief the SAB; such briefings would provide a diversity of technical perspectives on the strengths and limitations of the methodologies employed.

344. The SAB recognises the need for practical views on emerging and developing technologies. Viewing technologies using representations such as the Gartner hype-cycle can be valuable for separating possibilities from demonstrated capabilities. Likewise, many cutting edge technologies are developed in the private sector with significant monetary investment. Keeping abreast of patent filings, corporate partnerships, sources of investment, and business directions (including financial and forward looking information related to initial public offering filings) can provide useful insights into what may be possible, alongside what is a reliable capability, from these new technologies.

345. Recent initiatives within the Secretariat, including the creation of the post of Science Policy Adviser in 2012 to monitor developments in science and technology, have resulted in an increased interaction between the Secretariat and the SAB. The SAB recommends the Secretariat continues to augment and expand its capability to monitor and forecast developments in science and technology relevant to the Convention.

Education and outreach as a tool for the scientific review process

346. Education and outreach into scientific communities to raise awareness of the Convention and the norms of chemical disarmament was addressed by the SAB through its TWG on E&O from 2012 to 2014. Its recommendations led to the formation of the Advisory Board on Education and Outreach (ABEO). The ABEO is providing insight and advice on strategies for education and outreach to a broad range of stakeholders (EC-86/DG.29 C-22/DG.17, dated 4 October 2017; and their report on

the role of E&O in preventing the re-emergence of chemical weapons, ABEO-5/1, dated 12 February 2018). The SAB supports the ABEO.

347. The SAB recognises that many activities the Secretariat engages in provide opportunities for E&O, as the visibility of the OPCW in subject-specific forums provides an opportunity to raise awareness of the Convention and promote its norms. The scientific review process has enabled this.

348. To review the diversity of developments across scientific and industrial communities, understand where developments find application, and recognise where they intersect with the Convention, the SAB has benefited greatly from engagement with experts from a diversity of sectors. The technical nature of the discussions and areas of common scientific interest have raised awareness of the Convention. The SAB and the Secretariat will benefit from continuing to find opportunities to share experiences with relevant communities of experts, to help address future challenges.

349. It is imperative to maintain high levels of scientific literacy and to gather scientific insights by engaging with those driving technological change. The SAB encourages the Secretariat to seek opportunities to engage with technology developers and evaluate their tools under field conditions. The offer of feedback on capabilities under real-world conditions may help gain access to new technologies. This engagement would provide opportunity for further E&O.

350. The Secretariat might consider how it can engage in relevant innovation ecosystems. This might be enabled through research programmes involving the OPCW and DLs and through projects funded under Article XI programmes. The Secretariat might explore opportunities for engagement with scientific developers through the Article XI research support programme.

351. The SAB encourages the Secretariat to consider crowd-source and interactive forecasting approaches to facilitate engagement from technical experts outside familiar communities. Publications authored by the Secretariat and other technical stakeholders to the Convention, including the SAB, in the scientific literature provide additional visibility to chemical disarmament. Peer-reviewed scientific literature has the added value of establishing the scientific credibility of the technical expertise of the Secretariat. Methods and expertise accepted by scientific peer review demonstrate the scientific rigour and robustness necessary when results and data produced during implementation of the Convention transition to policy or legal forums. Publishing technical data related to IAUs would serve to consolidate and strengthen methods for verification of compliance to the Convention.

352. The Secretariat could usefully take opportunities to augment its E&O goals through the scientific review process. Benefits include raising awareness of the Convention across scientific communities, opportunities to provide feedback to technology developers on how their tools perform under field conditions, and a mechanism for the Secretariat to keep pace with technological change.

ACKNOWLEDGEMENTS

353. The SAB thanks the States Parties for their sustained support throughout the science and technology review process and for their attendance at "Science for Diplomats" and the SAB Chairperson and Vice-Chairperson for their briefings over the last five years. It also wishes to thank the OPCW Director-General, Ambassador Ahmet Üzümcü, for his inspirational leadership and role in promoting international diplomacy and international science in the service of peace, and for his constant encouragement and promotion of the Board's scientific work.

Annex 2

LIST OF REPORTS OF THE SCIENTIFIC ADVISORY BOARD AND ITS TEMPORARY WORKING GROUPS, AND RELATED DOCUMENTS OF THE SCIENTIFIC REVIEW PROCESS[22]

Report	Document Information	Availability at
Reports of, and Responses to Regular Sessions of the Scientific Advisory Board		
Report of the Scientific Advisory Board at its Twenty-Seventh Session	SAB-27/1, dated 23 March 2018	www.opcw.org/fileadmin/OPCW/SAB/en/sab-27-01_e_.pdf
Report of the Scientific Advisory Board at its Twenty-Sixth Session	SAB-26/1, dated 20 October 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab-26-01_e_.pdf
Report of the Scientific Advisory Board at its Twenty-Sixth Session - Corrigendum	SAB-26/1/Corr.1, dated 18 December 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab2601c1_e_.pdf
Response to the Report of the Twenty-Sixth Session of the Scientific Advisory Board	EC-87/DG.11, dated 25 January 2018	www.opcw.org/fileadmin/OPCW/SAB/en/ec87dg11_e_.pdf
Report of the Scientific Advisory Board at its Twenty-Fifth Session	SAB-25/1*, dated 31 March 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab2501_e_.pdf
The Impact of the Developments in Science and Technology in the Context of the Chemical Weapons Convention	EC-85/DG.8, dated 19 May 2017	www.opcw.org/fileadmin/OPCW/SAB/en/ec85dg08_e_.pdf
Report of the Scientific Advisory Board at its Twenty-Fourth Session	SAB-24/1, dated 28 October 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab-24-01_e_.pdf
Response to the Report of the Twenty-Fourth Session of the Scientific Advisory Board	EC-84/DG.9, dated 18 January 2017	www.opcw.org/fileadmin/OPCW/EC/84/en/ec84dg09_e_.pdf
Report of the Scientific Advisory Board at its Twenty-Third Session	SAB-23/1, dated 22 April 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab-23-01_e_.pdf
The Impact of the Developments in Science and Technology in the Context of the Chemical Weapons Convention	EC-82/DG.13, dated 7 June 2016	www.opcw.org/fileadmin/OPCW/SAB/en/ec82dg13_e_.pdf
Report of the Twenty-Second Session of the Scientific Advisory Board	SAB-22/1, dated 21 July 2015	www.opcw.org/fileadmin/OPCW/SAB/en/sab-22-01_e_.pdf
The Impact of Developments in Science and Technology in the Context of the Chemical Weapons Convention	EC-80/DG.7, dated 28 August 2015	www.opcw.org/fileadmin/OPCW/SAB/en/ec80dg07_e_.pdf
Report of the Twenty-First Session of the Scientific Advisory Board	SAB-21/1, dated 27 June 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-01_e_.pdf
Director-General's response to the Report of the Twenty-First Session of the Scientific Advisory Board	EC-77/DG.10, dated 5 September 2014	www.opcw.org/fileadmin/OPCW/SAB/en/ec77dg10_e_.pdf
Report of the Scientific Advisory Board at Its Twentieth Session	SAB-20/1, dated 14 June 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-01_e_.pdf
The Impact of Developments in Science and Technology in the Context of the Chemical Weapons Convention	EC-74/DG.1, dated 24 July 2013	www.opcw.org/fileadmin/OPCW/EC/74/en/ec74dg01_e_.pdf
Reports of the Scientific Advisory Board's International Workshop Series		
Report of the Scientific Advisory Board's Workshop on Trends in Chemical Production	SAB-26/WP.2, dated 19 October 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab-26-wp02_e_.pdf

22 List of English language documents available on the OPCW public website; see also Reports and Related documents of the Scientific Advisory Board at www.opcw.org/about-opcw/subsidiary-bodies/scientific-advisory-board/documents/.

Report	Document Information	Availability at
Report of the Scientific Advisory Board's Workshop on Emerging Technologies	SAB-26/WP.1, dated 21 July 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab26wp01_SAB.pdf
Report of the Scientific Advisory Board's Workshop on Chemical Warfare Agent Toxicity, Emergency Response and Medical Countermeasures	SAB-24/WP.2, dated 14 October 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab-24-wp02_e_.pdf
Report of the Scientific Advisory Board's Workshop on Chemical Forensics	SAB-24/WP.1, dated 14 July 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab24wp01_e_.pdf
Responses to Requests from the Director-General		
Response to the Director-General's Request to the Scientific Advisory Board to Provide Consideration on Which Riot Control Agents are Subject to Declaration Under the Chemical Weapons Convention	SAB-25/WP.1, dated 27 March 2017	www.opcw.org/fileadmin/OPCW/SAB/en/sab25wp01_e_.pdf
Declaration of Riot-Control Agents: Advice from the Scientific Advisory Board	S/1177/2014, dated 1 May 2014	www.opcw.org/fileadmin/OPCW/S_series/2014/en/s-1177-2014_e_.pdf
Response to the Director-General's Request to the Scientific Advisory Board to Provide Further Advice on Chemical Weapons Sample Stability and Storage	SAB-23/WP.2, dated 25 May 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab-23-wp02_e_.pdf
Response to the Director-General's Request to the Scientific Advisory Board to Provide Further Advice on Scheduled Chemicals	SAB-23/WP.1, dated 28 April 2016	www.opcw.org/fileadmin/OPCW/SAB/en/sab-23-wp01_e_.pdf
Response to the Director-General's Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection	SAB-22/WP.2/Rev.1, dated 10 June 2015	www.opcw.org/fileadmin/OPCW/SAB/en/sab-22-wp02_e_.pdf
Response to the Director-General's Request to the Scientific Advisory Board to Provide Further Advice on Assistance and Protection	SAB-21/WP.7, dated 29 April 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp07_e_.pdf
Reports of the Temporary Working Group on Investigative Science and Technology		
Summary of the First Meeting of the Scientific Advisory Board's Temporary Working Group on Investigative Science and Technology	SAB-27/WP.1, dated 26 February 2018	www.opcw.org/fileadmin/OPCW/SAB/en/sab-27-wp01_e_.pdf
Reports of the Temporary Working Group on Verification		
Verification Report of the Scientific Advisory Board's Temporary Working Group	SAB/REP/1/15, dated 11 June 2015	www.opcw.org/fileadmin/OPCW/SAB/en/Final_Report_of_SAB_TWG_on_Verification_-_as_presented_to_SAB.pdf
Summary of the Fourth Meeting of the Scientific Advisory Board's Temporary Working Group on Verification	SAB-22/WP.1, dated 1 October 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-22-wp01_e_.pdf
Summary of the Third Meeting of the Scientific Advisory Board Temporary Working Group on Verification	SAB-21/WP.6, dated 9 April 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp06_e_.pdf
Report of the Second Meeting of the Scientific Advisory Board Temporary Working Group on Verification	SAB-21/WP.1, dated 25 September 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp01_e_.pdf
Report of the First Meeting of the Scientific Advisory Board Temporary Working Group on Verification	SAB-20/WP.2*, dated 27 March 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-wp02__e_.pdf
Reports of the Temporary Working Group on Education and Outreach		
Education and Engagement: Promoting a Culture of Responsible Chemistry	SAB/REP/2/14, dated 28 November 2014	www.opcw.org/fileadmin/OPCW/SAB/en/Education_and_Engagement-v2.pdf
Report of the Third Meeting of the Scientific	SAB-21/WP.3, dated	www.opcw.org/fileadmin/OPCW/SAB

Report	Document Information	Availability at
Advisory Board's Temporary Working Group on Education and Outreach in Science and Technology Relevant to the Chemical Weapons Convention	7 January 2014	/en/sab-21-wp03_e_.pdf
Report of the Second Meeting of the Scientific Advisory Board's Temporary Working Group on Education and Outreach in Science and Technology Relevant to the Chemical Weapons Convention	SAB-20/WP.1, dated 25 February 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-wp01_e_.pdf
Report of the First Meeting of the SAB Temporary Working Group on Education and Outreach in Science and Technology Relevant to the CWC	Report is found in Annex 2 of SAB-18/1, dated 19 April 2012; meeting date was 12-13 April 2012	See Annex 2 of www.opcw.org/fileadmin/OPCW/SAB/en/sab-18-01_e_.pdf
Reports of the Temporary Working Group on the Convergence of Chemistry and Biology		
Convergence of Chemistry and Biology: Report of the Scientific Advisory Board's Temporary Working Group	SAB/REP/1/14, dated 26 June 2014	www.opcw.org/fileadmin/OPCW/SAB/en/TWG_Scientific_Advsiory_Group_Final_Report.pdf
Report of the Fourth Meeting of the Scientific Advisory Board, Temporary Working Group on the Convergence of Chemistry and Biology	SAB-21/WP.2, dated 25 November 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp02_e_.pdf
Report of the Third Meeting of the Scientific Advisory Board Temporary Working Group on the Convergence of Chemistry and Biology	SAB-20/WP.3, dated 11 April 2013	www.opcw.org/fileadmin/OPCW/SAB/en/sab-20-wp03_e_.pdf
Report of the Second Meeting of the SAB Temporary Working Group on the Convergence of Chemistry and Biology	Report is found in Annex 3 of SAB-19/1, dated 12 September 2012; meeting date was 6-7 September 2012	See Annex 3 of www.opcw.org/fileadmin/OPCW/SAB/en/sab-19-01_e_.pdf
Report of the First Meeting of the SAB Temporary Working Group on the Convergence of Biology and Chemistry	Report is found in Annex 3 of SAB-17/1, dated 23 November 2011; meeting date was 15-16 November 2011	See Annex 3 of www.opcw.org/fileadmin/OPCW/SAB/en/sab-17-01_e__2.pdf
Reports on Developments in Science and Technology to Earlier Review Conferences		
Report of the Scientific Advisory Board on Developments in Science and Technology for the Third Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention	RC-3/DG.1, dated 29 October 2012	www.opcw.org/fileadmin/OPCW/CSP/RC-3/en/rc3dg01_e_.pdf
Director-General's response to the Report of the Scientific Advisory Board on Developments in Science and Technology for the Third Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention	RC-3/DG.2, dated 31 January 2013	www.opcw.org/fileadmin/OPCW/CSP/RC-3/en/rc3dg02_e_.pdf
Report of the Scientific Advisory Board on Developments in Science and Technology	RC-2/DG.1, dated 28 February 2008	www.opcw.org/fileadmin/OPCW/CSP/RC-2/en/RC-2_DG.1-EN.pdf
Report of the Scientific Advisory Board on Developments in Science and Technology Corrigendum	RC-2/DG.1/Corr.1, dated 5 March 2008	www.opcw.org/fileadmin/OPCW/CSP/RC-2/en/RC-2_DG.1_Corr.1-EN.pdf
Report of the Scientific Advisory Board on Developments in Science and Technology	RC-1/DG.2, dated 23 April 2003	www.opcw.org/fileadmin/OPCW/CSP/RC-1/en/RC-1_DG.2-EN.pdf

Report	Document Information	Availability at
Miscellaneous Official SAB Documents Produced Between the Third and Fourth Review Conferences		
Ricin Fact Sheet	SAB-21/WP.5, dated 28 February 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp05_e_.pdf
Saxitoxin Fact Sheet	SAB-21/WP.4, dated 28 February 2014	www.opcw.org/fileadmin/OPCW/SAB/en/sab-21-wp04_e_.pdf

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