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REPORT OF THE SCIENTIFIC ADVISORY BOARD'S WORKSHOP ON TRENDS IN CHEMICAL PRODUCTION

1. EXECUTIVE SUMMARY

1.1 The OPCW Scientific Advisory Board (SAB) in cooperation with the Institute of Medical Research and Occupational Health (IMROH)[1] held an "International Workshop on Trends in Chemical Production", from 3 to 5 October 2017 in Zagreb, the Republic of Croatia.[2] The workshop was funded by the European Union[3] and organised under the auspices of the Croatian President Kolinda Grabar-Kitarović; the Ministry of Economy, Entrepreneurship and Crafts; and the City of Zagreb. It was the fourth and final workshop of a series[4] intended to inform the report of the SAB on developments in science and technology to the Fourth Review Conference[5] of the Chemical Weapons Convention (hereinafter, "the Convention") to be held in December 2018.

1.2 The past 70 years has seen extraordinary intellectual growth and socioeconomic impact from the field of chemistry (with both positive and negative examples to be found).[6] Chemistry itself has experienced continual change throughout its history, evolving into an area of science that provides significant opportunities for addressing

1 For additional information on IMROH, see: https://www.imi.hr/en/

2 OPCW Scientific Advisory Board Reviews Technological Developments and Trends in Chemical Production, 9 October 2017; www.opcw.org/news/article/opcw-scientific-advisory-board-reviews-technological-developments-and-trends-in-chemical-production/

3 This funding was provided through Project III (Science and Technology: Assessment of Developments in Science and Technology) of EU Council Decision (CFSP) 2015/259 dated 17 February 2015. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.043.01.0014.01.ENG

4 The three previous workshops of the series were: (1) "Chemical Forensics: Capabilities across the Field and the Potential Applications in Chemical Weapons Convention Implementation", held from 20 to 22 June 2016 in Helsinki, Finland (SAB/24-WP.1, dated 14 July 2016, www.opcw.org/fileadmin/OPCW/SAB/en/sab24wp01_e_.pdf) (2) "Chemical Warfare Agents: Toxicity, Emergency Response and Medical Countermeasures", held from 26 to 27 September 2016 in Paris, France (SAB-24/WP.2, dated 14 October 2016, www.opcw.org/fileadmin/OPCW/SAB/en/sab-24-wp02_e_.pdf). And (3) "Innovative Technologies for Chemical Security", held from 3 to 5 July 2017 in Rio de Janeiro, Brazil (SAB-26/WP.1, dated 21 July 2017, www.opcw.org/fileadmin/OPCW/SAB/en/sab26wp01_SAB.pdf)

5 Fourth Special Session of the Conference of the States Parties to Review the Operation of the Chemical Weapons Convention.

6 Reinventing chemistry; G. M. Whitesides; *Angew. Chem. Int. Ed.*; 2015, *54*, 3196 – 3209. DOI: 10.1002/anie.201410884.

current and future global challenges especially in disarmament[7]. Central to chemistry, is the discovery and production of chemicals, whether for the generation of new knowledge or for the socioeconomic pursuits, which have led to many societal benefits.[8] In the twenty-first century, it is often stated that scientific and technological change moves forward at accelerated pace with economic forces and the need for solutions to global problems driving technological change. An increasing convergence of scientific disciplines enables innovation and discovery, which is further strengthened through national and international and often industry-facilitated scientific collaboration and knowledge sharing. With technological changes manifesting across broad ranges of industries and sectors, especially relevant for the Convention, is the impact on the discovery and manufacturing of chemicals.

1.3 As described in the OPCW's 2017-2021 Medium-Term Plan,[9] with an end in sight for the completion of the destruction of declared chemical weapon stockpiles,[10] preventing the re-emergence of chemical weapons will assume greater importance in the work of the OPCW. As the Organisation transitions into a post-destruction phase, ensuring continued confidence in compliance with the obligations of the Convention will remain at the heart of its work.[11] Likewise, in the face of scientific, technological and socioeconomic change, it has been recognised by the SAB that methods and practices may need to adapt to changing realities.[12,13] In order to provide input and scientific guidance on technical dimensions of implementation and the impact to the Convention, understanding technological change related to chemical production and the driving forces behind such change is a critical aspect of the scientific review process.

1.4 To gain insights for providing practical scientific advice, the SAB invited experts from a variety of sectors of the chemical industry, experts engaged in research relevant to chemical synthesis and production technologies, and stakeholders involved in implementation of the Convention to share experiences and consider the short and long-term influence of technological change on chemical production. Topics included a review of the 20 years since entry into force of the Convention and the role chemical

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7 The Intersection of Science and Chemical Disarmament; B. Maneshi, J. E. Forman, *Science and Diplomacy*; 2015, 4(3), http://www.sciencediplomacy.org/perspective/2015/intersection-of-science-and-chemicaldisarmament

8 Nine for ninety; J. Fischman; *Chem. Eng. News*; 2013, *91(36)*; 26-27.

9 Medium-Term Plan of the Organisation for the Prohibition of Chemical Weapons 2017 – 2021 (EC-83/S/1 – C-21/S/1, dated 8 April 2016). Available at: www.opcw.org/fileadmin/OPCW/EC/83/en/ec83s01_c21s01_e_.pdf

10 A significant recent milestone being the completion of the full destruction of the 39,967 metric tons of chemical weapons possessed by the Russian Federation on 27 September 2017. See: www.opcw.org/news/article/opcw-director-general-commends-major-milestone-as-russia-completes-destruction-of-chemical-weapons-stockpile-under-opcw-verification/

11 See paragraphs 9-11 of footnote 8 above.

12 See for example: Verification, Report of the Scientific Advisory Board's Temporary Working Group (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

13 The potential for a need to change methods and practices has also been raised through OPCWs "vision paper", The OPCW in 2025: Ensuring a World Free of Chemical Weapons (S/1252/2015, dated 6 March 2015). Available at: www.opcw.org/fileadmin/OPCW/S_series/2015/en/s-1252-2015_e_.pdf

industry has played, developments across a variety of sectors of chemical industry, chemical and biobased production methods and technologies, technical aspects and approaches to industry verification under the Convention, and insights into activities that support discovery and production of chemicals (including chemical analysis and informatics).

1.5 The workshop was chaired by OPCW SAB Chairperson Dr Christopher Timperley. Dr Timperley and Dr Zrinka Kovarik (OPCW SAB member from IMROH) opened the workshop, and Mr Mario Antonić (the State Secretary of the Ministry of Economy, Entrepreneurship and Crafts of Croatia) delivered the opening address. The State Secretary welcomed participants to Zagreb, reaffirmed Croatia's commitment to the norms of the Chemical Weapons Convention and expressed his support for the work of the SAB, stating that "achievements in the field of chemistry should be exclusively used to the benefit of humans in a manner not forbidden by the Convention, by means of promoting free trade in chemical products as well as through international cooperation and exchange of scientific information". The opening session concluded with Dr Jonathan Forman (OPCW Science Policy Adviser and Secretary to the SAB) providing an overview of the programme, its intended outcomes, the Convention's science and technology review process, and the mechanism through which recommendations are made by the SAB.

1.6 From the workshop discussions, the following outcomes are submitted for consideration by the SAB at its Twenty-Sixth Session in October 2017:

(a) As technological advances related to the discovery and production of chemicals are adopted, a fit-for-purpose verification regime should maintain up to date operational knowledge of chemical (and biological) production methods (including aspects of synthesis and analysis). Recognising unusual processes or aspects of a laboratory or production facility that are inconsistent with allowable activities under the Convention is valuable for both prevention of re-emergence and post-event fact-finding. Training exercises and proficiency testing could usefully take into account such considerations. *See paragraphs 16.2-16.5 (with additional details in paragraphs 6.4-6.7, 7.2-7.9, 8.2-8.4, 9.2-9.3, 9.8-9.10, and 13.2-13.3).*

(b) In the face of a changing global security environment, the workshop drew attention to previous advice from the SAB's temporary working group (TWG) on Verification that considered risk-benefit approaches as a means to focus verification in areas that have greater risk to the intent and purpose of the Convention.[14] This could usefully include consideration of relevant chemicals not on the current schedules. *See subparagraphs 16.2(b), 16.3(c), 16,5(a), 5.4 and 6.4-6.7.*

(c) The workshop recognised a number of areas with potentially transferable learnings from industrial practices. These include approaches to trace analysis

[14] See recommendations 1-3, 9-10 and 15 of: Verification, Report of the Scientific Advisory Board's Temporary Working Group (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

and tools for chemical risk assessment. With reference to the latter, shared tools and chemical data sets have been developed to help with safer process and product design and for compliance under certain regulatory frameworks. These tools could usefully inform risk-benefit analysis and they may also be of relevance to those involved in chemical safety and security activities. *See subparagraphs 16.2(a) and 16.5(b) (with additional details in paragraphs 10.2-10.8, 14.2-14.3 and 15.1-15.4).*

(d) Several significant developments in the global chemical industry observed over the past 20 years were not recognised until they actually took shape (e.g. they were unanticipated in the years just before they happened). Engagement with technical experts from industry and more frequent review of industry focused research and development reports[15] would benefit the science review process and help keep the Technical Secretariat (hereinafter "the Secretariat") better informed. *See paragraphs 6.2-6.3, 7.2-7.9, 8.5-8.7, 9.4-9.7 and 11.2-11.6.*

(e) Synthesis tools being developed for chemical discovery purposes (complemented with machine learning approaches for predicting chemistry) can potentially 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 chemical classes. Such tools might be considered in the enhancement of laboratory capabilities for the implementation of the Convention.[16] *See paragraph 16.4 (with additional details in paragraphs 12.2-12.6 and 14.4-14.7).*

(f) The technical presentations and content of the workshop served as a reminder of the highly trans-disciplinary (convergent) nature of twenty-first century technology development, with scientific disciplinary convergence going well beyond the fields of chemistry and biology. This finding further supports the view that the scientific review process must engage broad scientific communities and look for opportunity in technological change to ensure that implementation of the Convention remains fit-for-purpose. Sharing of experience on science advice with other relevant disarmament communities (especially the Biological Weapons Convention stakeholders) should be encouraged. *See subparagraphs 16.2(a), 16.3(a), 16.5(a) and 14.3.*

(g) In the discussion of changing realities and the relevance of current verification practices, it was acknowledged that greater levels of science and technology

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15 For example, to review what has and has not remained constant in global research and development (including industry contributions) from 2013-2016, see:
(a) *2014 Global R&D Funding Forecast*; R&D Magazine; December 2013, https://abm-website-assets.s3.amazonaws.com/rdmag.com/s3fs-public/gff-2014-5_7%20875x10_0.pdf
(b) *2016 Global R&D Funding Forecast*; A supplement to R&D Magazine; Winter 2016, https://www.iriweb.org/sites/default/files/2016GlobalR%26DFundingForecast_2.pdf
(c) *2017 Global R&D Funding Forecast*; A supplement to R&D Magazine; Winter 2017, http://digital.rdmag.com/researchanddevelopment/2017_global_r_d_funding_forecast?pg=1#pg1

16 Upgrading The OPCW Chemical Laboratory to a Centre for Chemistry and Technology, S/1512/2017, dated 10 July 2017. Available at www.opcw.org/fileadmin/OPCW/S_series/2017/en/s-1512-2017_e_.pdf

engagement, and knowledge sharing amongst States Parties could also support the verification regime through the increased transparency such initiatives bring. *See subparagraph 16.5(b).*

2. AGENDA ITEM TWO – Adoption of the agenda

The workshop adopted the following agenda:

1. Opening of the session

2. Adoption of the agenda

3. *Tour de table* to introduce workshop participants

4. Establishment of a drafting committee

5. The Chemical Weapons Convention in Croatia and the 20th anniversary of the OPCW

   (a) 20 years of implementation of the Chemical Weapons Convention in Croatia

6. Chemical Industry and the Chemical Weapons Convention

   (a) Trends in the European and global chemical industry

   (b) Industry inspections and Chemical Weapons Convention policy: looking toward the future

7. Commodity and Platform Chemicals

   (a) Future directions of the modern chemical industry

   (b) Sustainability in chemistry

   (c) Chemical production by conversion of carbon to products through gas fermentation

8. Biomediated Production

   (a) Manufacturing: current status and future of biologicals in therapy

   (b) European biobased industries sector

9. Fine and Specialty Chemicals, and the Custom Synthesis Sector

   (a) Fine chemicals – current trends and challenges in industry

   (b) Custom synthesis in chemical production

(c) Trends in bioproduction and bioreactor design in relation to specialty chemical production

10. Pharmaceuticals

(a) Highly active pharmaceutical ingredients

(b) Safety and quality by design: minimising risk and environmental impact in pharmaceutical production

11. Agricultural Chemicals

(a) Pesticides: usage, production and future trends

12. Synthesis Tools

(a) Dial-a-Molecule

(b) Advanced techniques and approaches for small molecule synthesis

13. Nucleic Acids

(a) Next-generation DNA synthesis: a biological tool driving innovation in metabolic engineering

14. Chemical Analysis and Informatics

(a) Transferable learnings from a decade of mutagenic impurity analysis

(b) Machine learning in chemical synthesis

15. Regulatory Frameworks

(a) Regulation in the chemical industry

(b) Biomediated processes and industry verification under the Chemical Weapons Convention

16. Thematic discussions

(a) Advances in chemical production technologies and the synthesis of chemicals scheduled under the Chemical Weapons Convention

(b) Advances in biological production technologies and the synthesis of bioregulators and/or biological toxins

(c) The impact of current trends and future directions in chemical production on the Chemical Weapons Convention verification regime

(d) New synthesis tools and technologies for enhancing capabilities of OPCW Designated Laboratories

17. Closing remarks

18. Adoption of the report

3. AGENDA ITEM THREE – *Tour de table* to introduce workshop participants

A *tour de table* was undertaken to introduce workshop participants. The list of participants appears in the Annex of this report.

4. AGENDA ITEM FOUR – Establishment of a drafting committee

A drafting committee of SAB members was formed to prepare the draft report of the workshop.

5. AGENDA ITEM FIVE – The Chemical Weapons Convention in Croatia and the 20th anniversary of the OPCW

5.1 The workshop began with a reflection on the 20 years since entry-into-force of the Convention and the founding of the OPCW in 1997,[17] highlighting Croatia's role and contributions towards a chemical weapons free world. The session was moderated by Dr Zrinka Kovarik.

Subitem 5(a): 20 years of implementation of the Chemical Weapons Convention in Croatia

5.2 Ms Mirna Maravić (Ministry of Economy, Entrepreneurship and Crafts of Croatia) provided an overview of how Croatia has implemented the Convention, after becoming a State Party in 1997 and adopting the provisions of International Treaties, which prescribe the application of ratified International Treaties in the territory of the Republic of Croatia and their precedence over domestic law, into the Croatian Constitution. Croatia has taken an integrated approach to harmonisation of national legislation with the provisions of the Convention into national law; in 2013, the Croatian Parliament adopted the Chemicals Management Act (*Narodne novine* No. 127/13) with which the Republic of Croatia contributes to the development of safer chemical industry and the strengthening of global security by monitoring and preventing the spread of chemical weapons.

5.3 The Republic of Croatia established a National Authority (NA) for the Implementation of the Convention within the Ministry of Economy, Entrepreneurship and Crafts as the responsible national body for drafting relevant legislation. The NA is responsible for monitoring implementation of the provisions of the Convention, and coordination between the Republic of Croatia and the OPCW. The NA is also the focal point for relevant foreign entities and domestic institutions, agencies and industrial plants; and is comprised of representatives of Croatian ministries and

[17] More information on the 20th anniversary of the OPCW can be found at: https://20years.opcw.org/

administration. Ms Maravić provided an overview of the activities of the NA in implementation and promotion of the Convention.[18]

5.4 The session concluded with a review of the Republic of Croatia's 20 Years of collaboration with the OPCW, presented by Professor Zvonko Orehovec (University of Applied Science, Croatia). Professor Orehovec highlighted Croatia's contribution to the preparatory commission for the Chemical Weapons Convention in 1996, and discussed issues related to safety and security of chemical production and storage facilities, expressing concerns over possible acts of chemical sabotage and terrorism.[19] Related to these concerns, Professor Orehovec reviewed the outcomes of Croatia's organisation of the 1998 "Kutina '98" exercise which considered the consequence of an attack on a chemical facility; as well as the organisation under the auspices of the OPCW of the "Konavle 2001" and "Assistex I" exercises in 2001 and 2002.[20] These two international training exercises considered the scenarios of providing assistance and protection under the Convention following chemical incidents.

5.5 In the subsequent discussion, the following point was raised:

In light of current events and security concerns, as well as the establishment of OPCWs Rapid Response and Assistance Mechanism (RRAM),[21] lessons learned from the exercises held in 2001 and 2002 may be insightful to the Secretariat.

6. AGENDA ITEM SIX – Chemical Industry and the Chemical Weapons Convention

6.1 The workshop continued with perspectives on the global chemical industry and industry verification under the Convention.[22] The session was moderated by Mr Cheng Tang (OPCW SAB Vice-Chairperson).

Subitem 6(a): Trends in the European and global chemical industry

6.2 Dr René van Sloten (cefic[23]) discussed the evolution of chemical production after entry into force of the Convention. He described the world of 1997 as "tripolar", with

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18 For example, a recent event commemorating the 20th Anniversary of the OPCW: 20. godišnjica stupanja na snagu Konvencije o zabrani razvijanja, proizvodnje, gomilanja i korištenja kemijskog oružja I o njegovu uništenju; M. Maravić; *Izvještaji sa skupova, Kem. Ind.*, 2017, *66(7-8)*, 427–431. Available at: http://silverstripe.fkit.hr/kui/assets/Uploads/Izvjestaji-sa-skupova-430-431.pdf

19 Military, technical and defence-security standards on industrial facilities protection in case of terrorism and military attack; Z. Orehovec; in C. Dishovsky, A. Pivovarov (eds); *Counteraction to Chemical and Biological Terrorism in East European Countries*; Springer Science + Business Media B. V., 2009, 55-63.

20 The Exercises "Kutina '98" and "Assistex 1" - Lessons Learned or Learning Lessons?; Z. Orehovec; in: S. Bokan Z. Orehovec Z (eds); *Proceedings of the Second World Congress on Chemical, Biological and Radiological Terrorism*; Croatia, 2003, 312-317.

21 (a) Guidelines for States Parties Requesting a Rapid Response and Assistance Mission (S/1429/2016, dated 17 October 2016), available at: www.opcw.org/fileadmin/OPCW/S_series/2016/en/s-1429-2016_e_.pdf (b) Establishment of a Rapid Response Assistance Team (S/1381/2016, dated 10 May 2016), available at: www.opcw.org/fileadmin/OPCW/S_series/2016/en/s-1381-2016_e_.pdf

22 For an introduction to Industry Verification under the Convention, see "OPCW - The Verification regime under Article VI of the Convention"; S. Hohn; 2017; https://prezi.com/hq3dts_v2aho/opcw-the-verification-regime-under-article-vi-of-the-convention-13-march-2017/

the European Union (EU), Japan and the United States of America as the top three chemical producing regions; the world has since witnessed the emergence of multiple new production platforms in Brazil, India, the Middle East, South East Asia, and the Republic of Korea. Roughly 40% of world chemical production now occurs in China and a shale gas boom has revived the chemical industry in the United States of America. These developments have influenced global trade patterns and may over time lead to regional blocs each specialising in production of chemicals where they have competitive advantages. The EU chemical industry's share has roughly halved in the past two decades, resulting in the EU chemical industry seeking to move up the innovation ladder by developing products that provide solutions to global challenges that include climate change, energy, water, health, and food. Dr van Sloten described how industry is looking to transform itself in the face of increasing global competition, requiring a visionary EU industrial policy strategy.[24]

6.3 In the subsequent discussion, the following points were raised:

(a) It is currently assumed that the chemical industry will see continued growth, with a further shift of balance to regions outside the EU. Participants noted however, that some of the trends discussed (specifically growth of chemical industry in Asia, and North American shale gas revival) were unforeseen in the years just prior to these developments, suggesting that changes in industry are not totally predictable, and reinforcing the idea that developments in the chemical industry worldwide are important considerations within the scientific review process.

(b) Reducing energy cost is critical for competiveness. Production plants built with new technologies to help in this regard will continue to be installed. However, adoption of energy-efficient processes may be cost-prohibitive if they are not coupled with the generation of value-added products.

(c) The growth in chemicals in regions such as the EU is in innovation and speciality (high value) chemicals. It was however, noted that societal acceptance of innovative chemical products, regulatory constraints and international competition, exert influence on the success of this strategy.

Subitem 6(b): Industry inspections and Chemical Weapons Convention policy: looking toward the future

6.4 Dr Stephanie Dare-Doyen (Senior Policy Officer in the OPCW Office of Strategy and Policy) introduced workshop participants to the industry verification regime and policies. The OPCW has conducted over 3,500 inspections since the entry into force of the Convention in chemical industry sites declared under Article VI.[25] On-site

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23 European Chemical Industry Council, for additional information on cefic, see: http://www.cefic.org/

24 *The European Chemical Industry, Facts and Figures*, cefic, 2016; available at http://www.cefic.org/Facts-and-Figures/

25 Statistics on OPCW verification activities are available through the annual reports of the organisation, www.opcw.org/documents-reports/annual-reports/

inspection activities mainly focus on declared schedule 2 or 3 chemicals[26] and the production by synthesis of discrete organic chemicals (DOCs).[27]

6.5 As noted in the executive summary of this report, verification methods and practices may need to adapt to changing realities, and there is also a need to ensure that industry inspections are conducted in an effective, efficient and consistent manner. This is not a new objective: many initiatives have been launched, including the 2010-2012 programme for the review of the Article VI verification regime (S/1066/2013, dated 11 February 2013)[28] and the TWG on Verification which produced 18 recommendations in 2015.[29]

6.6 Future challenges include adapting to advances in science and technology; this might usefully be viewed as an enhancement of techniques and equipment,[30] but any changes considered may also create new policy issues. For example, the case for the detection of impurities related to the production of Schedule 1 unavoidable by-products, for which the Secretariat has developed a dedicated policy.[31] Moreover, the misuse of chemicals by non-State actors is a reality that cannot be ignored. How the verification regime might be adapted to answer the numerous concerns about the use of chlorine gas and other chemicals as chemical weapons is an open question. Taking into due account the broad scope of Article VI provisions,[32] maybe it is time to revisit on-site inspection procedures and focus on toxic chemicals with significant risk of misuse in an inspected site, instead of primarily focusing on declared chemicals and related activities?

6.7 In the subsequent discussion, the following points were raised:

(a) Industry representatives at the workshop inquired about the scope of Secretariat-led initiatives, asking how decisions would be taken in regard to the ideas presented, and how such ideas would be discussed amongst relevant stakeholders. Dr Dare-Doyen noted discussions take place regularly with States Parties through informal consultations on chemical industry issues (the

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26 Schedules 2 and 3 of the Convention's Annex on Chemicals, www.opcw.org/chemical-weapons-convention/annexes/annex-on-chemicals/ An infographic guide to the schedules is also available at: https://www.opcw.org/fileadmin/OPCW/Science_Technology/Guide_to_Schedules.pdf

27 A DOC is defined in paragraph 4 of Part 1 of the Convention's Verification Annex as "any chemical belonging to the class of chemical compounds consisting of all compounds of carbon except for its oxides, sulfides and metal carbonates, identifiable by chemical name, by structural formula, if known, and by Chemical Abstracts Service registry number, if assigned". www.opcw.org/chemical-weapons-convention/annexes/verification-annex/part-i/

28 Refinements in the Conduct of Inspections to Improve the Consistency, Effectiveness, and Efficiency of the Article VI Verification Regime, available at: www.opcw.org/fileadmin/OPCW/S_series/2013/en/s-1066-2013_e_.pdf

29 A quick reference guide to the recommendations of the TWG on Verification is available at: www.opcw.org/fileadmin/OPCW/SAB/en/VER_Poster_5102015.pdf

30 See for example: Innovative Technologies for Chemical Security (SAB-26/WP.1, dated 21 July 2017). Available at: www.opcw.org/fileadmin/OPCW/SAB/en/sab26wp01_SAB.pdf

31 Procedure for handling cases of Schedule I chemicals as Unavoidable By-products (S/1272/2015, dated 1 May 2015).

32 The Contribution of Article VI to States Parties' Efforts to Counter Terrorism (S/1387/2016, dated 19 May 2016). Available at: www.opcw.org/fileadmin/OPCW/S_series/2016/en/s-1387-2016_e_.pdf

"Industry Cluster") and the SAB noted that its previous recommendations regarding verification were recently presented to States Parties through the open-ended working group on future priorities (OEWG-FP).[33]

(b) Questions were raised regarding declarations related to riot control agents and central-nervous system acting agents (specifically, can the two types of chemicals be distinguished?). Participants were briefed on the SAB's recent advice on riot-control agents,[34,35] that while non-binding, it provides guidance on recognising chemicals that would fit the definition of a riot-control agent as defined by Article II, paragraph 7 of the Convention.[36]

7. AGENDA ITEM SEVEN – Commodity and Platform Chemicals

7.1 Professor Ferruccio Trifiró moderated a session focusing on technological change and its drivers in large scale chemical production.

Subitem 7(a): Future directions of the modern chemical industry

7.2 Professor Fabrizio Cavani (University of Bologna, Italy) discussed future directions in the chemical industry, noting that chemicals represent one of the largest and most research and development (R&D) intensive manufacturing sectors in all of the advanced economies, whose patterns of innovation can profoundly impact economic growth. For example, the European chemical industry supplies virtually all sectors of the economy and accounts for around 18% of the total sales of chemicals in the world.

7.3 The presentation highlighted areas of significant change occurring in the European chemical industry with the aim of lowering environmental impact, while maintaining competitiveness.[37,38] This included insights into the challenges that chemical industry

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33 The briefing by SAB Vice-Chair Mr Cheng Tang on 31 January 2017 is available at: https://www.opcw.org/fileadmin/OPCW/SAB/en/20170131_SAB_Briefing_to_Open_Ended_Working_Group_Future_Priorities.pdf

34 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). Available at: www.opcw.org/fileadmin/OPCW/SAB/en/sab25wp01_e_.pdf

35 An infographic summary of this advice is available at: www.opcw.org/fileadmin/OPCW/Science_Technology/riot_control_agents_poster.pdf

36 A riot-control agent is defined as "[a]ny chemical not listed in a Schedule, which can produce rapidly in humans sensory irritation or disabling physical effects which disappear within a short time following termination of exposure"; www.opcw.org/chemical-weapons-convention/articles/article-ii-definitions-and-criteria/

37 (a) *Taking the European chemical industry into the circular economy*; Accenture Consulting; 2017. Available at: https://www.accenture.com/us-en/insight-circular-economy-european-chemical-industry(b) *Competitiveness of the European chemical industry*; cefic; 2015. Available at: http://www.cefic.org/Documents/RESOURCES/Reports-and-Brochure/Competitiveness-of-the-European-chemical-industry-2014.pdf (c) *The future of the European chemical industry*; KPMG International, 2010. Available at: http://bulgarien.ahk.de/fileadmin/ahk_bulgarien/Dokumente/EuroChem_Europe_Final_01.pdf

38 *Industry 4.0 and the chemicals industry*; S. V. Thienen, A. Clinton, M. Mahto, B. Sniderman; Deloitte University Press, June 2016. Available at: https://dupress.deloitte.com/dup-us-en/focus/industry-4-0/chemicals-industry-value-chain.html

expects to face over the next few decades in order maintain its strategic role.[39] He provided examples of replacing conventional fossil-based chemical processes, with new processes based on bio-platform molecules derived from renewable raw materials;[40] and presented life cycle analysis (LCA) comparisons for several chemical production technologies.[41]

7.4 In the subsequent discussion, the following points were raised:

(a) It was noted that 85-90% of feedstock remains petrochemical, despite the interest and attention given to renewable feedstocks, leading to questions on what drives a transition to the use of biobased feedstocks. LCA methods were noted as valuable tools for assessing whether new processes are likely to take hold (based on economic and practical viability).

(b) Additional considerations in adoption of renewable feedstocks were also discussed. Cost increases to consumers can limit marketability, and production considerations must take into account economically-viable sources of raw materials which can regionally limit certain types of production processes.

Subitem 7(b): Sustainability in chemistry

7.5 Dr Detlef Maennig (International Chemical Council Associations[42]) provided an overview of the role of sustainability in the modern chemical industry.[43] He noted that sustainability is not a fashion or a marketing gimmick, let alone a cost driver; rather it is a driver for innovation, profitability[44] and social progress. In this regard, he provided examples of how sustainability-driven companies are more successful,[45] and how sustainability can ensure license to operate, operative excellence (which includes risk mitigation) and profitable growth. Dr Maennig described how the flagship

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39 *Chemical industry vision 2030: a European perspective*; ATKearney; 2012, https://www.atkearney.com/chemicals/article?/a/chemical-industry-vision-2030-a-european-perspective

40 *Chemicals and Fuels from Bio-Based Building Blocks*; F. Cavani, S. Albonetti, F. Basile, A. Gandini; Wiley, 2016. ISBN: 978-3-527-33897-9.

41 (a) Butadiene from biomass, a life cycle perspective to address sustainability in the chemical industry; D. Cespi, F. Passarini, I. Vassura, F. Cavani; *Green Chem*; 2016, *18*, 1625. DOI: 10.1039/C5GC02148K. (b) LCA of 1,4-butanediol produced via direct fermentation of sugars from wheat straw feedstock within a territorial biorefinery; A. Forte, A. Zucaro, R. Basosi, A. Fierr; *Materials (Basel)*; 2016, *9(7)*, 563. DOI: 10.3390/ma9070563 (c) Glycerol as feedstock in the synthesis of chemicals: a life cycle analysis for acrolein production; D. Cespi, F. Passarini, G. Mastragostino, I. Vassura, S. Larocca, A. Iaconi, A. Chieregato, J.-L. Dubois, F. Cavani; *Green Chem*; 2015, *17*, 343. DOI: 10.1039/C4GC01497A.

42 For additional information on the International Chemical Council Associations (ICCA), see https://www.iccaworld.org/

43 Vision 2050: the new agenda for business; World Business Council for Sustainable Development, http://www.wbcsd.org/Overview/About-us/Vision2050

44 *Pathways to a low-carbon economy: Version 2 of the global greenhouse gas abatement cost curve*; McKinsey 2013, https://www.mckinsey.com/business-functions/sustainability-and-resource-productivity/our-insights/pathways-to-a-low-carbon-economy

45 *Climate action and profitability: CDP S&P 500 Climate Change Report 2014*; CDP, 2014.

programmes Responsible Care® [46] and Global Product Strategy[47] help to drive sustainability in the chemical industry and the many ways that chemical industry contributes to the United Nations Sustainable Development goals.[48,49]

7.6 In the subsequent discussion, the following points were raised:

(a) Sustainability can serve as a way for companies to demonstrate corporate responsibility and planetary citizenship. This also has a connection to the Convention through Article VII, paragraph 3: "Each 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." This link between the Convention and the goals of sustainability initiatives may provide opportunities to raise awareness about the Convention through recognition of how sustainability supports its norms and objectives.

(b) Examples were discussed of long-term benefits for companies embracing sustainability. However, it was acknowledged that companies changing their practices in this direction can experience short-term financial pressures that might act as a disincentive.

(c) There are many fields of science that use sustainability goals to guide research. Green chemistry for example, is a field that generates scientific knowledge and innovations that support and have potential benefit (whether immediate or forward looking) to the objectives of the Convention (e.g. Article VII, paragraph 3). It should be recognised however, that technological adoption of new research requires the developments be economically viable and practical. Not all innovations arising from scientific advances will meet such criteria.

Subitem 7(c): Chemical production by conversion of carbon to products through gas fermentation

7.7 Dr Sean Simpson (Chief Scientific Officer and Founder, LanzaTech,[50] USA) presented the work his company has been pioneering in chemical production through

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46 For additional information on Responsible Care®, see http://www.cefic.org/Responsible-Care/

47 For additional information on Global Product Strategy, see http://www.eurochemgroup.com/en/global-product-strategy-gps/

48 For further information on the United Nations Sustainable Development Goals, see: http://www.un.org/sustainabledevelopment/sustainable-development-goals/

49 (a) Global Chemical Industry Contributions to the Sustainable Development Goals; International Council of Chemical Associations (ICCA); January 2017. Available at: https://www.icca-chem.org/wp-content/uploads/2017/02/Global-Chemical-Industry-Contributions-to-the-UN-Sustainable-Development-Goals.pdf (b) The European chemical industry contribution to the United Nations Sustainable Development Goals, http://www.cefic.org/sustainability/UN-Sustainable-Goals/ (c) European chemical industry's contribution to sustainable development; P. Barthelemy, E. Agyeman-Budu; *Current Opinion in Green and Sustainable Chemistry*; 2016, *1*, 28-32. DOI: 10.1016/j.cogsc.2016.08.002.

50 For additional information on LanzaTech, see: http://www.lanzatech.com/

gas fermentation.[51] He described anthropogenic climate change as a driving force for the development of technologies that enable non-traditional, sustainable or waste feedstocks to be used for the production of fuels, chemicals and energy. Technologies allowing energy production with no terminal release of greenhouse carbon dioxide (CO_2) are now mature and out-compete traditional power generation processes economically. This advance not only impacts the energy sector, but has also enabled an accelerated transition to sustainable electrical mobility, thus challenging the role of hydrocarbons as the dominant source of road transportation fuel. Even with the advance of electrical mobility, a source of carbon is still required for the aviation sector and for the production of chemicals. Gas fermentation enables a broad range of high volume, low value waste streams to be transformed into both commodity fuels and speciality chemicals. These gas feedstocks either exist as direct by-products of essential industrial processes or through the gasification of agricultural and societal solid waste streams into syngas.[52,53] In this way gas fermentation is a vital bridge in the effort to create value from waste and enable the perpetual capture of greenhouse carbon in valuable materials.

7.8 Dr Simpson described the platform being commercialised by LanzaTech that allows continuous biological production of fuels and an array of chemical intermediates from gases at scale.[54] The first commercial facilities are currently under construction with the process having been demonstrated with live feeds of waste gas from numerous processes and industries (including steel mills and energy production). Implications arising from the development of technologies that enable the transformation of non-traditional waste feedstocks to commodity chemicals are expected to result in a more distributed chemical production infrastructure than we currently see today.

7.9 In the subsequent discussion, the following points were raised:

(a) The demonstration of platform chemical production using waste gas streams from sources such as steel manufacturing, landfill and energy production (e.g. CO_2) facilities opens up the potential for decentralisation of chemical production. Furthermore, the biobased processes involved do not require agriculture to produce feedstocks and they recycle waste products of energy consumption. Wide-scale adoption of such processes could be disruptive to the current trends that are expected for chemical industry.

(b) Complexity in a traditional chemical manufacturing plant is in the infrastructure ("hardware"), while complexity in a biomediated plant is in the biology ("software"). The availability of a variety of gas fermenting bacteria

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51 Gas fermentation—a flexible platform for commercial scale production of low-carbon-fuels and chemicals from waste and renewable feedstock; F. M. Liew, M. E. Martin, R. C. Tappel, B. D. Heijstra, C. Mihalcea, M. Köpke; *Front. Microbiol*; 2016, *7*, 1-28. DOI: 10.3389/fmicb.2016.00694.

52 Synthesis gas chemistry and synthetic fuels; Syngaschem BV. (n.d.); http://www.syngaschem.com/syngaschem

53 Syngas Biorefinery and Syngas Utilization; S. De Tissera, M. Köpke, S. D. Simpson, C. Humphreys, N. P. Minton, P. Dürre P.; in: *Advances in Biochemical Engineering/Biotechnology*, 2017, Springer, Berlin, Heidelberg. DOI: 10.1007/10_2017_5.

54 For a technical overview of the LanzaTech process, see: http://www.lanzatech.com/innovation/technical-overview/

that can be substituted into fermenters could potentially allow production plants to respond to market conditions.

8. AGENDA ITEM EIGHT – Biomediated production

8.1 This session focused on biobased technologies, was moderated by Professor Isel Alonso.

Subitem 8(a): Manufacturing: current status and future of biologicals in therapy

8.2 Dr Florian Wurm (Chief Scientific Officer and President, ExcellGene SA,[55] Switzerland) provided an overview of production capabilities for biologicals.[56] His overview described how biologicals have been used for therapy and prevention of disease for centuries and how the tremendous boost provided by the DNA-based revolution in biotech has given rise to a dominance of biologicals amongst new drugs being developed and approved; these drugs being predominantly antibody and antibody-like molecules. Such molecules are of complex structure and very large (in comparison to typical drugs like antibiotics or pain killers). They are produced, for the smaller category, in bacteria (insulin, for example), or in animal cells in bioreactors for the more complex proteins (for which bacterial cells may lack the biomolecular machinery necessary to properly fold such proteins). He noted that Chinese Hamster Ovary (CHO) cells are used to produce over 70% of all biologicals on the market today.[57]

8.3 Dr Wurm described the production and uses of antibodies or similar molecules, and explained how the industry has developed and discussed its future directions. He provided insights into the critical complexities of making such molecules, particularly now that patents for the first multibillion US dollar products have expired, and companies are competing for market share in the production of biosimilars (a biosimilar is a biological medicine which is highly similar to another biological medicine already licensed for clinical use).[58]

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55 For additional information on ExcellGene SA, see: http://www.excellgene.com/

56 (a) Medium and process development for high yield, high-density suspension cultures: from low throughput Spinner flasks to high throughput milliliter reactors; M. De Jesus, F. M. Wurm; *Bioprocess International*, 2009, *7(1)*, 13-19. (b) 25 years of recombinant proteins from reactor-grown cells : where do we go from here?; D. L. Hacker, M. De Jesus, F. M. Wurm; *Biotechnol Adv.*, 2009, DOI: 10.1016/j.biotechadv.2009.05.008. (c) Manufacturing of biopharmaceuticals and implications for biosimilars; F. M Wurm; *Kidney Blood Press Res.*, 2007, *30(1)*, 6-8. (d) Production of recombinant protein therapeutics in cultivated mammalian cells; F. M. Wurm; *Nature Biotechnology*, 2004, *22(11)*, 1393-1398.

57 (a) Cloning of CHO cells, productivity and genetic stability—a discussion; F. M. Wurm; M. J. Wurm; *Processes*; 2017, *5(2)*, 20. DOI:10.3390/pr5020020. (b) CHO history, CHO evolution and CHO genomics – an unsolvable enigma; F. M. Wurm; *Hauser and Wagner: Animal Cell Biotechnology De Gruyter*; 2014, 38-60. (c) CHO quasispecies—implications for manufacturing processes; F. M. Wurm; *Processes*; 2013, *1(3),* 296-311. DOI:10.3390/pr1030296.

58 (a) Factors influencing the economics of biosimilars in the US; S. R. Mehr, R. A. Brook; *Journal of Medical Economics*; 2017. DOI: 10.1080/13696998.2017.1366325. (b) Biosimilars part 1: proposed regulatory criteria for FDA approval; C. L. Ventola; *Pharmacy and Therapeutics*; 2013, *38(5)*, 270-274, 277, 287. (c) Biosimilars part 2: potential concerns and challenges for p&t committees; C. L. Ventola; *Pharmacy and Therapeutics*; 2013, *38(6)*, 329-335.

8.4 In the subsequent discussion, the following points were raised:

(a) Current technologies can routinely produce 1-5 g/litre of a biological, with production batch sizes of up to 200-300 g.

(b) Dr Wurm indicated that the majority of biological production is done through batch processes, although continuous processing methods are possible. In the latter case, batches must still be defined for regulatory and quality purposes. Batches in a batch process are defined by material, batches in a continuous process are defined by the run time of the process.

(c) Water quality was noted as a significant issue for biological production, requiring ratios of 1:10 for reactor fill: purification water usage; changes in water quality can have severe impact on the quality and yield of product.

(d) Questions were raised about toxin production. While this is possible, it requires selection of suitable cell lines to avoid the toxin killing the host cell. Antibodies linked to toxins for medical use are becoming more common, however many of these materials are produced by chemical coupling.[59]

(e) The technology described might in future be applied to production of antibody-based medical countermeasures against poisoning by toxins[60] and/or central nervous system (CNS) acting agents.[61]

Subitem 8(b): European biobased industries sector

8.5 Ms Andrea Božić (Head of Education and Information Center, Saponia d.d.,[62] Croatia) presented an overview of the European biobased industry sector[63] and

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59 (a) Strategies and challenges for the next generation of antibody–drug conjugates; A. Beck, L. Goetsch, C. Dumontet, N. Corvaïa; *Nature Reviews Drug Discovery*, 2017, *16*, 315–337. DOI: 10.1038/nrd.2016.268. (b) Development of commercial-ready processes for antibody drug conjugates; X. Hu, E. Bortell, F. W. Kotch, A. Xu, B. Arve, S. Freese; *Org. Process Res. Dev.*, 2017, 21(4), 601-610. DOI: 10.1021/acs.oprd.7b00023.

60 (a) Recent advances in the development of vaccines against ricin; R. N. Brey III, N. J. Mantis, S. H. Pincus, E. S. Vitetta, L. A. Smith, C. J. Roy; *Journal Human Vaccines & Immunotherapeutics*; 2016, *12(5)*, 1196-1201. DOI: 10.1080/21645515.2015.1124202. (b) Progress and challenges associated with the development of ricin toxin subunit vaccines; D. J. Vance, N. J. Mantis; *Expert Review of Vaccines*, 2016, 15(9), 1213-1222. DOI: 10.1586/14760584.2016.1168701.

61 (a) An advance in prescription opioid vaccines: overdose mortality reduction and extraordinary alteration of drug half-life; A. Kimishima, C. J. Wenthur, B. Zhou, K. D. Janda; *Chem. Biol.*, 2017, *12(1)*, 36–40. DOI: 10.1021/acschembio.6b00977. (b) Vaccines for Opioid Addiction; M. D. Raleigh, P. R. Pentel; in: I. Montoya (ed); *Biologics to Treat Substance Use Disorders*, 2016 Springer, Cham, 37-63. DOI: 10.1007/978-3-319-23150-1_4.

62 For additional information on Saponia d. d., see: http://www.saponia.hr/hr/

63 Bio-based Industries JU: a €3.7 billion partnership between the EU and the Bio-based Industries Consortium, https://www.bbi-europe.eu/

bioeconomy.[64] Ms Božić explained that in Europe, the biobased industry sector refers to production and extraction of renewable biological resources ('biomass') and their conversion into food and feed; bio-based products[65,66] (such as timber, fibre, chemicals or bioplastics) and bioenergy (for example, firewood, biofuels and/or biogas). The biobased industry encompasses a wide range of sectors, in particular agriculture, forestry, fisheries, food processing, energy, pulp and paper, chemicals, and biotechnology. The bioeconomy has emerged over the past decade as a knowledge-driven concept aimed at meeting a number of today's challenges, in particular creating jobs and growth, moving away from fossil fuels and feeding a growing human population.[67] Biobased products and materials are just one part of it. Biobased chemical products can be structurally identical to those obtained from fossil-based feedstock, but there is a further potential to develop new biobased products and materials that are not currently accessible through fossil-based feedstock.[68] Economically viable biobased products have been demonstrated with equal or superior properties compared to fossil-based products or materials; and the potential of such products and materials spans the entire product spectrum of the chemical industry.

8.6 Ms Božić highlighted how the bioeconomy can improve resource efficiency and is a key element in achieving the broader concept of a circular, integrated, renewable economy. The bioeconomy can also be a driver of research and innovation as demonstrated by recent developments in bioscience and biotechnology, especially in areas such as biobased materials and agriculture, with biorefineries that can produce a variety of products such as fuels, chemicals, plastics, heat and electricity.[69] Ms Božić noted that a transition to a biobased industrial sector could have both positive and negative socioeconomic impact on the cost of food, commodities and land; farmers' revenues; trade balances (due for instance to the diversification of energy sources and reduced reliance on fossil fuel imports); or land usage (in particular outside the EU, as a result of indirect land-use change). Ms Božić noted that the regions currently active in developing their bioeconomies will establish themselves as knowledge and technology leaders in the field.

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64 (a) *Position on Bioeconomy Strategy and Action Plan Review and Revision*; EU Commission Expert Group on Bio-based Products; 2017, http://ec.europa.eu/docsroom/documents/25042 (d) A bioeconomy for Europe; G. LaRouche; 2016 (Presentation), http://cor.europa.eu/en/events/Documents/KEP/01_DG_RTD.F.1_KEP%20Bioeconomy%20Seminar_GL_29_4_2016_.pptx (c) The Industrial Bioeconomy (Agricol group), http://www.theagricolagroup.com/bioproducts.html.

65 For additional information on biobased products in the EU, see: http://ec.europa.eu/growth/sectors/biotechnology/bio-based-products_en

66 See for example: The importance of fungi and of mycology for a global development of the bioeconomy; L. Lange; *IMA Fungus*; 2012, *3(1)*, 87-92. DOI: 10.5598/imafungus.2012.03.01.09.

67 Pathways to shape the bioeconomy; C. Priefer, J. Joerissen, O. Froer; *Resources*; 2017, *6*, 10. DOI: 10.3390/resources6010010.

68 *Strategic Innovation and Research Agenda*, SUSCHEM (European Technology Platform for Sustainable Chemistry), 2015, available at: www.suschem.org/files/library/SIRA_SusChem_Def_Web-NEW-LOGO_v03.pdf

69 *Bio-based chemicals: value added products from biorefineries*; IAE Bioenergy – Task 42 Biorefinery; 2012, available at: http://www.ieabioenergy.com/wp-content/uploads/2013/10/Task-42-Biobased-Chemicals-value-added-products-from-biorefineries.pdf

8.7 In the subsequent discussion, the following points were raised:

Trends in commercial investment in bioproducts were further considered. Cost increases on products (which are ultimately passed on to consumers) that are biobased have disincentivised some companies from investing. This may have longer term impact on innovation and specialty chemical sectors in affected regions.

9. AGENDA ITEM NINE – Fine and Specialty Chemicals, and the Custom Synthesis Sector

9.1 Dr Koji Takeuchi moderated a session focused on speciality chemicals, fine chemicals and custom synthesis.

Subitem 9(a): Fine chemicals – current trends and challenges in industry

9.2 Dr Olaf Burkhardt (Director Global Supply Chain Management, Healthcare, Evonik Industries AG[70]) provided the workshop with an overview of the fine chemicals sector. He noted that the fine chemicals industry is in a central position of the value chain, converting commodities into substances of high purity for the specialty chemical industry (with as much as 50% of fine chemicals going toward pharmaceutical production).[71] Fine chemical manufacturing processes often still follow classical organic synthesis in stirred tank reactors, but new technologies are increasingly being adopted (with biobased production noted as being very limited).[72] Moving away from classical organic synthesis requires innovative R&D capabilities in combination with a broad variety of competencies. Dr Burkhardt discussed challenges to flexibility and economic viability in the fine chemical sector that have arisen from increasing requirements for quality and environmental regulation. He further noted that for pharma- and agrochemical businesses, reliable supply chains and competent partnerships are drivers of where these businesses purchase critical fine chemicals (indicating that the lowest cost options may not be viable if quality and reliability needs and requirements cannot be met).

9.3 In the subsequent discussion, the following points were raised:

(a) In fine chemical manufacture, production of each product needs to be optimised and developed. This requires engineering expertise and an emphasis on development over research.

(b) In regard to adoption of new technologies, it was noted that as the technologies become more sophisticated and the compounds more active, maintenance and safety require more resources. These resources and their implications would be considered by industry before a given product is taken forward, in some cases limiting the adoption of new types of equipment.

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70 For additional information on Evonik Industries AG, see http://corporate.evonik.com/

71 *Fine chemicals: The Industry and the Business*; P. Pollack; John Wiley & Son, Inc.; 2011, ISBN: 978-0-470-62767-9.

72 (a) *Chemical Technology*; P. Wasserscheid; A. Jess; Wiley-Vch Verlag Gmbh; 2016, ISBN: 978-3-527-67061-1. (b) *Practical Process Research & Development*; N. G. Anderson; Academic Press, 2000, ISBN: 9780080514482.

(c) For a company to differentiate itself in the current chemical industry, it must have competencies that allow rapid innovation. Such competencies are recognised as value drivers in fast changing markets. However, the ability to innovate may be constrained by regulatory requirements.

Subitem 9(b): Custom synthesis in chemical production

9.4 Dr Tony Bastock (Chairman Contract Chemicals Ltd., United Kingdom[73]) presented an overview of the role of custom synthesis in the chemical industry and global chemical commerce. Custom manufacturing is the process of making products or product lines to a customer's unique specifications. Toll manufacturing is the process of a company providing its raw materials or semi-finished goods to a third-party custom/contract manufacturing organisation (CMO), which often has specialised equipment or chemistry, to carry out the manufacturing processes on its behalf using those materials or goods for a fee or toll. Contract manufacturing is either custom or toll manufacturing, with a terms and conditions contract in place. Dr Bastock noted that the market for contract manufacturing of active pharmaceutical ingredients is currently estimated to be €11.8 billion.

9.5 Contract manufacturing becomes advantageous when companies need to increase their production of chemical products beyond their current capacity, or when developing new products that they want to test in the market before investing in a new plant. It is used also when companies do not have the equipment and/or chemistry to produce a new product, want to outsource upstream materials and still produce the final compound in-house, want local production for local markets (common for products that do not travel well), or need building blocks (intermediates) for products or formulations manufactured to bespoke specifications.

9.6 The presentation discussed some of the practical aspects of custom manufacturing with Dr Bastock noting that incoming processes are often not production plant ready, and need laboratory work to modify them to fit the CMO's plant. This will often require non-disclosure agreements to protect intellectual property. Regulatory requirements also impact the ability to adopt a new process at the CMO (and compliance may be the responsibility of the manufacturer in addition). For example, a full hazard study might be required to confirm health and safety compatibility of the CMO's plant and process.

9.7 In the subsequent discussion, the following points were raised:

(a) Successful CMOs are often strong in specific areas with capabilities to produce chemicals on the kilogram to tonne scale. Expertise in specific classes of fine chemicals is common for CMOs.

(b) The capability to convert a CMO between classes and types of products varies with the core business, as many facilities are optimised toward the needs of specific customers, which may limit overall flexibility. The risk for equipment to be used clandestinely to produce toxic chemicals, including chemical

[73] For additional information on Contract Chemicals Ltd., UK, see: http://www.contract-chemicals.com/

warfare agents, is higher for kilogram and smaller scales, as equipment pertaining to this scale of production is more flexible and modular (this assumes producing material to cause harm vs. stockpiling large quantities).

(c) For the CMO, the business model is to "sell time" on the production equipment. Innovation for speeding up processes (to have more time to sell to more customers) and reducing costs is important.

Subitem 9(c): Trends in bioproduction and bioreactor design in relation to specialty chemical production

9.8 Dr Ir. Nico M. G. Oosterhuis (Celltainer Biotech BV, the Netherlands[74]) described bioreactor designs that are used for the manufacture of speciality chemicals and biologicals. He reminded the participants that biochemical production has been carried out for centuries starting from the production of beer and wine with yeast in ancient times.[75] Following the Second World War, biochemical production became more professionalised and industrialised and products such as antibiotics, (food) chemicals, enzymes, and amino acids were produced using stainless steel, stirred reactors with volumes of 100 m^3 or larger. Throughout the 1970's and 1980's, more dedicated processes were developed, including the production of single-cell proteins from microbes that can feed off methane from natural gas in processes requiring special reactor designs.[76] Today as a result of advances in genetic modification technologies, biochemical production has been adopted for foods and animal feed, but also in the chemical and pharmaceutical sectors. Processes for the production of amino acids (feed ingredients) can be scaled to bioreactor volumes of 500 m^3 and above. Production of fine chemicals, such as farnesene,[77] (bio)succinic acid[78] and lactic acid[79] are fully industrialised and run at reactor scales of 100 m^3 and larger. These compounds can be used for further chemical modifications, allowing flexibility for the upstream part of the process.

9.9 In the (bio)pharmaceutical industry, smaller but more volume intensive processes are often used. The productivity of cell lines has increased and there is increasing adoption of continuous processing. During the last decade, single-use technologies,

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74 For additional information on Celltainer Biotech BV, see: http://celltainer.com/

75 An infographic timeline of biotechnology is available at: http://www.biotechweek.org/wp-content/uploads/2016/10/Europabio-Timeline21x21HR.pdf

76 Single cell protein; G. L. Solomons, J. H. Litchfield; *Critical Reviews in Biotechnology*; 1983, *1*, 21-58. DOI: 10.3109/07388558309082578.

77 Industrial fermentation of renewable diesel fuels; P. J. Westfall, T. S. Gardner; *Current Opinion in Biotechnology*, 2011, *22(3)*, 344–350. DOI: 10.1016/j.copbio.2011.04.023.

78 (a) Succinic acid; J. H. Ahn, Y.-S. Ang, S. Yup Lee; Chapter 17 in *Industrial Biotechnology: Products and Processes*; C. Wittmann and J. C. Liao (eds.), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. DOI: 10.1002/9783527807833.ch17. (b) Succinic acid production derived from carbohydrates: an energy and greenhouse gas assessment of a platform chemical toward a bio-based economy; B. Cok; I. Tsiropoulos; A. L. Roes, M. K. Patel; *Biofpr*; 2014, *8(1)*, 16–29. DOI: 10.1002/bbb.1427.

79 Lactic acid bacteria, in Industrial Biotechnology: Microorganisms; L. Ruiz-Rodríguez, J. Bleckwedel, M. Eugenia Ortiz, M. Pescuma, F. Mozzi; Chapter 11 in *Industrial Biotechnology: Products and Processes*; C. Wittmann and J. C. Liao (eds), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. DOI: 10.1002/9783527807796.ch11.

including single-use bioreactors have been successfully introduced.[80] Single-use equipment requires less infrastructure, is less costly in terms of investment, and allows great flexibility with applications to a range of products. Single-use technologies are commonly used in such facilities produce complex (bio)chemicals, toxins and/or viruses.

9.10 In the subsequent discussion, the following points were raised:

(a) Bioproduction at industrial facilities often relies on dedicated process equipment and is constrained by operational resource requirements (such as biomass availability). Dr Oosterhuis expressed the opinion that such facilities are of low risk to the Convention in terms of possible conversion to weapon producing facilities.

(b) As noted for traditional chemical processing in the discussion following Dr Bastock's presentation, it is the small scale processing that would be easiest to adopt to prepare toxic materials intended for harmful purposes. Disposable fermentation equipment would be considered dual-use in this regard, and Dr Oosterhuis indicated the products of Celltainer Biotech BV were subject to the Dutch export control regime.

10. AGENDA ITEM TEN – Pharmaceuticals

10.1 Dr Renate Becker-Arnold moderated a session focused on the production of pharmaceuticals.

Subitem 10(a): Highly active pharmaceutical ingredients

10.2 Dr Andreas Beyeler (F. Hoffmann - La Roche AG, Switzerland[81]) provided an overview on the production requirements for active pharmaceutical ingredients (APIs) discussing both the regulatory and working standard aspects. These include FDA[82] and EMEA[83] quality standards, and cGMP,[84] with processes and validation methods being registered and regulated.

10.3 As a result of progress towards personalised health care, targeted drug design and increased regulatory pressures for bringing drugs to market, the production of APIs has been trending toward higher activity (HAPIs) and smaller quantity. HAPIs are solid materials and cover a wide variety of chemical products (Calcitriol,[85]

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80 (a) Single-use in the biopharmaceutical industry: a review of current technology impact, challenges and limitations; A. G. Lopes; *LLB Global Health Solutions Ltd.*; 2015, *93*, 98-114; DOI: 10.1016/j.fbp.2013.12.002. (b) Single-use disposable technologies for biopharmaceutical manufacturing; A. A. Shukla, U. Gottschalk; *KBI Biopharma*; 2013, *31(3),* 147-154. DOI: 10.1016/j.tibtech.2012.10.004.

81 For additional information on F. Hoffmann - La Roche AG, see: https://www.roche.com/

82 FDA: US Food and Drug Administration, https://www.fda.gov/

83 EMEA: European Medicines Evaluations Agency, http://www.ema.europa.eu/ema/

84 cGMP = current Good Manufacturing Practice, for additional information see https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm

85 Calcitriol, https://pubchem.ncbi.nlm.nih.gov/compound/calcitriol#section=Top

Cobimetinib[86] and Vismodegib[87] were shown as examples). The commonality across the products are high efficacy at point of use.

10.4 Dr Beyeler explained how the trend towards compounds with higher activity impact technical installations and the new approaches and technical solutions required for production of HAPIs. He described how planning phase concepts are defined to meet production, cleaning, health and safety standards (which take occupational exposure limits into consideration) and how these ideas were realised accordingly in the design of a small-scale manufacturing facility.[88]

10.5 In the subsequent discussion, the following points were raised:

(a) Facilities that produce HAPIs are designed for containment of the product as a way to protect workers and the product itself from contamination. The equipment requires properly trained and skilled operators (especially for cleaning and maintenance); it would not be considered "easy" to use by untrained persons.

(b) As new facilities are built on existing plant sites, space constraints will dictate designs. This has resulted in standalone buildings that do not look like traditional chemical manufacturing facilities, as tanks and pipes may be placed underground and behind walls, giving the facility the look of a normal building from the outside.

(c) Schedule 2 in the Convention's Annex on Chemicals lists two pharmaceutical precursors: 2B(8), 2,2-diphenyl-2-hydroxyacetic acid; and 2B(9), 3-quinuclidinol. These precursors are not commonly used in API facilities as developments in palladium chemistry[89] have made a broader variety of molecular structures accessible for developing effective pharmaceuticals.

Subitem 10(b): Safety and quality by design: minimizing risk and environmental impact in pharmaceutical production

10.6 Dr Ernest Meštrović (Teva Group[90], Croatia) provided an overview of how safety and quality requirements are incorporated into pharmaceutical production processes using the concept of "safety by design". Dr Meštrović noted that there are more than 70,000 products in the chemical industry, with the most complex products being pharmaceuticals[91] of which there are over 10,000 drugs and more than 160,000

86 Cobimetinib, https://pubchem.ncbi.nlm.nih.gov/compound/16222096#section=Top

87 Vismodegib, https://pubchem.ncbi.nlm.nih.gov/compound/24776445#section=Top

88 An approach to the commercial production of highly active pharmaceutical ingredients; A. Beyeler, R. Wilhelm, B. Brodbeck; *Chimia*; 2016, 70(9), 596-603. DOI: 10.2533/chimia.2016.596.

89 (a) Reactions of the 21st Century: two decades of innovative catalyst design for palladium-catalyzed cross-couplings; P. Gildner, T. J. Colacot; *Organometallics*, 2015, 34(23), 5497–5508. DOI: 10.1021/acs.organomet.5b00567. (b) From noble metal to Nobel Prize: palladium-catalyzed coupling reactions as key methods in organic synthesis; X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, M.; *Angewandte Chemie International Edition*, 2010, *49*, 9047–9050. DOI: 10.1002/anie.201006374.

90 For additional information on the Teva Group, see: http://www.tevapharm.com

91 (a) Big data from pharmaceutical patents: a computational analysis of medicinal chemists' bread and butter; N. Schneider, D M. Lowe, R. A. Sayle, M. A. Tarselli, G. A. Landrum; *J. Med. Chem.*; 2016, *59*

associated materials. Taking a drug from concept to patient begins with screening around 10,000 compounds and the entire development process can take as long as 14 years and cost billions of dollars, all stages being under regulatory control. Ensuring that safety considerations are taken into account is critical as problems arising years into the process could require starting over again.

10.7 "Safety by design"[92] is based on the concept of "quality by design".[93] In quality by design, one builds quality into development (material attributes, process parameters, time/equipment/operations). This same approach can be used for safety and to assess chemical hazards.[94] Safety evaluations before scale up involve the measurement of thermodynamic parameters using calorimetric techniques and computational tools to help model and guide decisions.

10.8 In the subsequent discussion, the following point was raised:

(a) Thermodynamic measurements[95] provide critical data for evaluating if a process can be safely scaled up. Such considerations would potentially be of value for certain types of risk assessment regarding large scale chemical production and production equipment design requirements.

11. AGENDA ITEM ELEVEN – Agricultural Chemicals

11.1 Ms Barbara Hedler (OPCW Industry Verification Branch) moderated a session focused on pesticides.

Subitem 11(a): Pesticides: usage, production and future trends

11.2 Dr Syed K. Raza provided a presentation on pesticides, looking at where they are used, how they are manufactured, and the current trends in the sector. Pesticides are substances that are meant to control pests,[96] they are defined by the Food and Agriculture Organization of the United Nations (FAO) as "any substance or mixture of substances intended for preventing, destroying, or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals, causing harm during or otherwise interfering with the production, processing, storage,

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(9), 4385–4402; DOI: 10.1021/acs.jmedchem.6b00153 (b) The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates; S. D. Roughley, A. M. Jordan; *J. Med. Chem.*; 2011, *54 (10),* 3451–3479. DOI: 10.1021/jm200187v.

92 Application of safety by design methodology in evaluating process safety for a Duff reaction using predictive process simulators; F. Jović, A. Sučec, I. Nekola, D. Čavužić, E. Marcelić, E. Meštrović; *Org. Process Res. Dev.*; 2015, *19(9),* 1268–1273. DOI: 10.1021/acs.oprd.5b00174.

93 A review on quality by design; V. Mogal, J. Dusane; P. Borase, P. Thakare, S. Kshirsagar; *Pharmaceutical and biological evaluations*; 2016, *3(3),* 313-319. ISSN: 2394-0859. (b) Pharmaceutical product development: A quality by design approach; K. Pramod, M. Abu Tahir, N. A. Charoo, S. H. Ansari, J. Ali; *Int J Pharm Investig*; 2016, *6(3),* 129–138. DOI: 10.4103/2230-973X.187350.

94 *Bretherick's Handbook of Reactive Chemical Hazards*; P.G. Urben; Elsevier Ltd; 2017, ISBN: 978-0-08-100971-0.

95 Recent advances and potential applications of modulated differential scanning calorimetry (mDSC) in drug development; M. M. Knopp, K. Löbmann, D. P. Elder, T. Rades, R. Holm; *Eur J Pharm Sci.*, 2016, *25(87)*, 164-73. DOI: 10.1016/j.ejps.2015.12.024.

96 For further information on pesticides see: https://www.epa.gov/ingredients-used-pesticide-products/basic-information-about-pesticide-ingredients

transport, or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances that may be administered to animals for the control of insects, arachnids, or other pests in or on their bodies".[97] The definition includes substances intended for use as plant growth regulators, defoliants, desiccants, as well as agents for thinning fruit or preventing the premature fall of fruit. Pesticides are applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

11.3 Pesticides are typically classified by target organism (e.g., herbicides, insecticides, fungicides, rodenticides, and pediculicides (for treatment of lice).[98] Chemicals used as pesticides include organochlorines, organophosphates, and carbamates; Dr Raza noted that the organochlorine insecticide DDT is also still used in parts of the developing world.[99] There are new trends toward safer biopesticides that can include microbes and biochemicals (hormones for example).[100] While plant-derived pesticides, or "botanicals" (pyrethroids, rotenoids, nicotinoids, and a fourth group that includes strychnine and scilliroside,[101] for example), are seeing increased development, world-wide pesticide use primarily relies on unnatural chemicals.

11.4 Pesticides are used to control organisms considered to be harmful to plants, animals and humans, such as disease-transmitting and stinging insects (such as mosquitoes, fleas, bees, wasps or ants). Pesticides are also used to prevent sickness in humans caused by mouldy food or diseased produce. Herbicides are used to clear roadside weeds, trees and brush, or to eliminate invasive plant species that may cause ecological and/or environmental damage. Other applications include preventing infrastructure damage such as that caused by termites or mould in buildings. In grocery stores and food storage facilities, pesticides are applied to manage rodents and insects. The use of a pesticide carries associated risks, as exposure can induce both acute and delayed health effects,[102] ranging from irritation of skin and eyes to severe effects on the nervous system, mimicking hormones causing reproductive problems, as well as cancers.[103] This necessitates that those working with pesticides follow proper usage procedures that decrease the risks to acceptable levels (which are defined within a regulatory framework).

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97 International code of conduct on the distribution and use of pesticides; Food and Agriculture Organization of the United Nations; 1990, http://www.fao.org/docrep/005/y4544e/y4544e00.htm

98 Pesticides and health risks; R. C. Gilden, K. Huffling, B. Sattler; *J. Obstet. Gynecol. Neonatal Nurs.*; 2010, *39(1)*, 103-110. DOI: 10.1111/j.1552-6909.2009.01092.x.

99 Global trends in the production and use of DDT for control of malaria and other vector-borne diseases; H. van den Berg, G. Manuweera, F. Konradsen; *Malaria Journal*, 2017, 16:401. DOI: 10.1186/s12936-017-2050-2.

100 Additional information on classes of pesticides can be found at: http://www.epa.gov/pesticides/about/types.htm

101 *Pesticide Profiles: Toxicity, Environmental Impact, and Fate*; M. A. Kamrin; CRC Press, 1997. ISBN 9781566701907.

102 U.S. Environmental Protection Agency, Pesticides: Health and Safety. National Assessment of the Worker Protection Workshop #3, August 30, 2007.

103 (a) For further information on human health issues related to the use of pesticides, see: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/human-health-issues-related-pesticides (b) Cancer health effects of pesticides: systematic review; K. L. Bassil, C. Vakil, M. Sanborn, D. C. Cole, J. S. Kaur, K. J. Kerr; *Can. Fam. Physician*; 2007, *53(10)*, 1704-1711.

11.5 Despite the risks, pesticides are an economically important class of chemicals. They are used to prevent crop losses to insects and other pests; and not using pesticides has the potential to reduce crop yields,[104] increase food prices, create job losses and increase world hunger.[105] To meet the demands for pesticide use, these chemicals are produced in large quantities in both developed and developing economies, with approximately 2.5 billion kilograms used worldwide per annum.[106] Dr Raza described production processes (which may follow GMP) and regulatory aspects of the development, manufacture and handling of pesticide compounds, noting that pesticide development requires toxicity testing, especially clinical studies and assessments of environmental fate.

11.6 In the subsequent discussion, the following points were raised:

(a) Pesticide development focuses on formulations to improve handling, storage, application, and safety. Dr Raza noted that there are more than 20,000 pesticide products currently available worldwide.

(b) Education in handling pesticides is critical for all those who use these chemicals. Improper usage has led to significant health impacts to farm workers, especially in developing countries.

(c) Evaluation and removal of specific pesticides from use is an on-going process – it falls under the purview of the Stockholm Convention.[107]

(d) Sustainability concepts are also making inroads into agriculture, with integrated crop management (ICM)[108] and implementation of good agricultural practices (GAP).[109] Information related to these initiatives may be of interest to chemical safety and security-relevant best practices.

12. AGENDA ITEM TWELVE – Synthesis Tools

12.1 Dr Christophe Curty moderated a session focused on the development of new tools for performing chemical synthesis.

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104 Effects of organic fertilization and pesticide application on growth and yield of fieldgrown rice for 10 years; S. Kuniuki; *Japanese Journal of Crop Science*; 2001, *70(4)*, 530-540. DOI: 10.1626/jcs.70.530.

105 *Economic impact of reduced pesticide use in the United States*; R. Knutson; Agricultural and Food Policy Center, Texas A&M University; 1999, *99(2)*.

106 Pesticides use and exposure, extensive worldwide; M. C. R. Alavanja; *Rev. Environ. Health*; 2009, *24(4)*, 303-309.

107 The Stockholm Convention on Persistent Organic Pollutants, for additional information see: http://chm.pops.int/TheConvention/Overview/tabid/3351/Default.aspx

108 For additional information in ICM, see: http://www.cabi.org/about-cabi/cabi-centres/switzerland/integrated-crop-management/

109 For additional information on GAP, see: https://www.ams.usda.gov/services/auditing/gap-ghp

Subitem 12(a): Dial-a-Molecule

12.2 Professor Richard Whitby (University of Southampton) presented the Dial-a-Molecule project,[110,111] a UK Engineering and Physical Sciences Research Council (EPSRC)[112] funded Grand Challenge network with the vision: "In 20-40 years, scientists will be able to deliver any desired molecule within a timeframe useful to the end-user, using safe, economically viable and sustainable processes." The network was established through a competitive process with strong support from industry, and currently has around 50% non-academic membership. The network has run many meetings over the past 6 years, mostly hosted at industrial sites, aimed at bringing together the disparate disciplines needed to tackle the Grand Challenge.[113] A roadmap has been published which identifies many of the advances needed,[114] of which the most fundamental is that organic synthesis needs to change to a data driven discipline with much greater use of automation and computation. Professor Whitby described Dial-a-Molecule, the work it has carried out to promote various aspects of its roadmap, how it is bringing different disciplines together, and funded projects including multiphase continuous reactors: aerobic conditions (air as an oxidising agent),[115] factory in a fume hood (process intensification)[116] and closed loop for sustainable chemical manufacture.[117]

12.3 In the subsequent discussion, the following points were raised:

(a) Emphasis for research on new tools for organic synthesis is on discovery not scale-up and production. The tools developed might potentially be of great value for the complex synthesis of pharmaceuticals.

(b) A key theme in Professor Whitby's presentation was that synthesis needs to change; he noted that 'the whole field of computers has passed it by'. Synthesis is more than an organic chemistry problem, its biggest challenge is adopting better use of informatics and artificial intelligence and big data – with the need to make synthesis predictable.

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110 For additional information on Dial-a-Molecule, see: www.dial-a-molecule.org

111 Organic synthesis: the robo-chemist; M. Peplow; *Nature*; 2014, *512*, 20-22. DOI: 10.1038/512020a.

112 For additional information on EPSRC, see: https://www.epsrc.ac.uk/

113 See for example, Dial-a-molecule workshop: computational prediction of reaction outcomes and optimum synthetic routes; K. J. Kilpin, J. M. Goodman, A. P. Johnson, R. J. Whitby; *Chemistry Central Journal*; 2015, *9:49*. DOI: 10.1186/s13065-015-0129-9.

114 Transforming synthesis, enabling science, Roadmap for Synthesis in the 21st Century; EPSRC. Available at: http://generic.wordpress.soton.ac.uk/dial-a-molecule/wp-content/blogs.dir/sites/50/2012/10/Dial-a-Molecule-Roadmap.pdf

115 A review of research in this area is available in: Aerobic oxidations in flow: opportunities for the fine chemicals and pharmaceuticals industries; A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. (M) Hii, G. J. Hutchings, G, L. Brett, S. Kuhn, S. P. Marsden; *React. Chem. Eng.*; 2016, *1*, 595-612. DOI: 10.1039/C6RE00155F.

116 For further information see: http://gtr.rcuk.ac.uk/projects?ref=EP%2FL003325%2F1

117 For further information see: http://gtr.rcuk.ac.uk/projects?ref=EP%2FL003309%2F1

(c) Realisation of Dial-a-Molecule requires input from many disciplines, and would lead to substantial academic economic and societal benefits if successful.

(d) Enablers for realising Dial-a-Molecule include: researchers seeing value in the data from reactions not just products, electronic notebooks, the use of Design of Experiments (DOE), the use of computational tools (including DFT[118]), incentives for developing reactions not just discovering them, publishing the full scope of research on reactions and making data available (including through the use of pre-print servers). This is all about collecting and sharing better data.

(e) 3D printing has also been used as an enabler for innovation in laboratory equipment.[119]

Subitem 12(b): Advanced techniques and approaches for small molecule synthesis

12.4 Dr Kerry Gilmore (Max Planck Institute of Colloids and Interfaces, Germany) reviewed the increasing use and applications of continuous flow reactor technologies in synthetic chemistry.[120] He explained that while continuous chemical processes have attracted both academic and industrial interest, virtually all APIs – and small molecules in general – are produced using multiple distinct batch processes. To date, methods for the divergent, multi-step continuous production of customisable small molecules are not available.

12.5 Dr Gilmore discussed the development of a chemical assembly system, where robust flow-reaction modules are linked together, such that multiple medicines can be produced by a single system. These reaction modules allow high-yielding transformations (with no or water-soluble by-products) and can be linked to subsequent reactors or via an inline workup/biphasic extraction. Several examples of such modules were discussed, in particular efforts with singlet oxygen generation and

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118 Density Function Theory. The use of this method to study sulfur mustard has been previously discussed by the SAB, see: Report of the Scientific Advisory Board at its Twenty-Fifth Session (SAB-25/1*, dated 30 March 2017), paragraph 9.19. Available at: www.opcw.org/fileadmin/OPCW/SAB/en/sab2501_e_.pdf See also: Investigation of Polysulfide Mustard Analogues and Reactive Intermediates from Levinstein Mustard by Density Functional Theory (DFT); M.-M. Blum. www.opcw.org/fileadmin/OPCW/Science_Technology/poster_MustardDFT.pdf

119 (a) Recent advances in analytical chemistry by 3D printing; B. Gross, S. Y. Lockwood, D. M. Spence; *Anal. Chem.*; 2017, *89(1),* 57–70. DOI: 10.1021/acs.analchem.6b04344. (b) The €100 lab: a 3D-printable open-source platform for fluorescence microscopy, optogenetics, and accurate temperature control during behaviour of zebrafish, Drosophila, and Caenorhabditis elegans; A. M. Chagas , L. L. Prieto-Godino, A. B. Arrenberg, T. Baden; *PLOS Biology*; 2017, *15(7).* DOI: 10.1371/journal.pbio.2002702. (c) Developments of 3D printing microfluidics and applications in chemistry and biology: a review; Y. He, Y. Wu, J. Z. Fu, Q. Gao, J. J. Qiu*; Electroanalysis*; 2016, *28*, 1658. DOI: 10.1002/elan.201600043. (d) (b) Open labware: 3-D printing your own lab equipment; T. Baden; A. M. Chagas, G. Gage, T. Marzullo, L. L. Prieto-Godino, T. Euler; *PLOS Biology*; 2015, *13(5)*. DOI: 10.1371/journal.pbio.1002086.

120 The hitchhiker's guide to flow chemistry; M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger; *Chem. Rev.*, 2017, *117 (18),* 11796–11893. DOI: 10.1021/acs.chemrev.7b00183.

its utilisation for the ambient and low temperature oxidation of amines.[121] These concepts can be extended even further in the design of new approaches towards chemical synthesis, maximising flexibility and accessing multiple products and APIs from single systems called Chemical Assembly Systems.[122]

12.6 In the subsequent discussion, the following points were raised:

(a) While modular approaches to chemistry/automation are not new to chemistry (e.g. DNA, peptides) expanding them to broader types of reactions and improving reproducibility is needed.

(b) Flow reactors offer new ways to perform novel chemical transformations and to do chemistry and reduce safety risks.

(c) Coupling continuous flow reactors with analytical methods and chip based assay platforms, opens up new possibilities for real-time synthesis and activity screening of new compounds.[123] With suitable development, such systems may enable the potential to screen toxicity (coupling to an "organs screening chips"[124]) or even material reactivity (for gathering information on what may react with toxic industrial chemicals for informing the kind of environmental samples that might be collected in investigative missions).

13. AGENDA ITEM THIRTEEN – Nucleic Acids

Subitem 13(a): Next-generation DNA synthesis: a biological tool driving innovation in metabolic engineering

13.1 Dr Pål Aas moderated a session looking at automated synthesis of nucleic acids.

13.2 Dr Devin Leake (Head of DNA Synthesis, Ginkgo Bioworks, United States of America[125]) reviewed automated nucleic acid synthesis. He described the dramatic improvements in cost and scale of DNA synthesis that have advanced capabilities and

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121 Factors influencing the regioselectivity of the oxidation of asymmetric secondary amines with singlet oxygen; D. Ushakov, M. Plutschack, K. Gilmore; Chemistry, 2015, 21(17), 6528-6534. DOI: 10.1002/chem.201500121.

122 Chemical Assembly Systems: layered control for divergent, continuous, multistep syntheses of active pharmaceutical ingredients; D. Ghislieri; K. Gilmore; P. H. Seeberger; *Angew. Chem. Int. Ed.*; 2015, *54(2)*, 678-682. DOI: 10.1002/anie.201409765.

123 (a) Real-time biological annotation of synthetic compounds; J. G. Christopher, B. K. Hua, J. M. Wawer, J. P. Knowles, S. D. Nelson, O. Verho, S. Dandapani, B. K. Wagner, P. A. Clemons, K. I. Booker-Milburn, Z. V. Boskovic, S. L. Schreiber; *J. Am. Chem. Soc.;* 2016, *138(28),* 8920–8927. DOI: 10.1021/jacs.6b04614. (b) Current status and future prospects for enabling chemistry technology in the drug discovery process; S. W. Djuric, C. W. Hutchins, N. N. Talaty; *F1000Res*; 2016, *5*, 2426. DOI: 10.12688/f1000research.9515.1.

124 (a) Organ-on-a-chip for assessing environmental toxicants; S. Cho, J.-Y. Yoon; *Current Opinion in Biotechnology*, 2017, 34-42. DOI: 10.1016/j.copbio.2016.11.019. (b) The role of microfluidics for organ on chip simulations; A. U. R. Aziz, C. Geng, M. Fu, X. Yu, K. Qin, B. Liu; *Bioengineering*, 2017, *4(2)*, 39. DOI: 10.3390/bioengineering4020039 (c) Special issue: Organs-on-Chips & 3D-bioprinting technologies for personalized medicine; Y. M. Elçin; *Stem Cell Rev and Rep.*, 2017, *13*, 319-320. DOI: 10.1007/s12015-017-9744-2. (b)

125 For additional information on Ginkgo Bioworks, see: http://www.ginkgobioworks.com/

facilitated new industrial applications. Specifically, progress in synthesis quality has been significant, enabling the generation of longer length DNA, and thus whole genome creation.[126] Dr Leake discussed how with these highly-developed capabilities, potential biosecurity risks have been raised[127,128] how the ubiquitous access of DNA synthesis provides a unique challenge for risk mitigation strategies.

13.3 In the subsequent discussion, the following points were raised:

(a) Compatibility of synthetic DNA in a host cell is difficult to predict and will determine whether or not a modified organism is functional.

(b) Virus assembly is possible, but direct synthesis of long DNA strands (long constructs) is difficult.[129]

14. AGENDA ITEM FOURTEEN – Chemical Analysis and Informatics

14.1 Professor Roberto Martínez-Álvarez moderated a session intended to look at analytical and informatics technologies that are important in supporting chemical production activities.

Subitem 14(a): Transferable learnings from a decade of mutagenic impurity analysis

14.2 Dr David Elder (formerly of GlaxoSmithKline, and now a chemistry, manufacturing, and control (CMC) Consultant) reviewed the evolution of the International Conference on Harmonization (ICH) M7 guidelines: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.[130,131] His overview covered some of the significant analytical challenges required for the analysis of volatile and highly reactive analytes in complex matrices, and pointed out that similar analysis approaches have been used for traces of mutagenic compounds in pharmaceuticals and samples containing mutagenic

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126 On DNA and transistors; R. Carlson; 2016, http://www.synthesis.cc/synthesis/2016/03/on_dna_and_transistors

127 The International Consortium for Gene Synthesis (ICGS) is a consortium of companies that aim to support government efforts to prevent the misuse of gene synthesis, http://www.genesynthesisconsortium.org/

128 See for example: Options for synthetic DNA order screening, revisited; D. DiEuliis, S. R. Carter, G. K. Gronvall; *Msphere*; 2017, *2(4)*, e00319-17. DOI: 10.1128/mSphere.00319-17.

129 Large-scale de novo DNA synthesis: technologies and applications; S. Kosuri, G. M. Church; *Nature Methods*, 2014, 11, 499–507. DOI: 10.1038/nmeth.2918.

130 M7(R1) addendum to ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk; United States Food and Drug Administration (FDA); 2015, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464285.pdf

131 See also: Classification according to chemical structure, mutagenicity to Salmonella and level of carcinogenicity of a further 39 chemicals tested for carcinogenicity by the U.S. National Toxicology Program; R. W. Tennant, J. Ashby; *Mutat Res.*, 1991, *257(3)*, 209-227. DOI: 10.1016/0165-1110(91)90002-D.

chemical warfare agents.[132] Dr Elder also discussed the use of inductively coupled plasma mass spectrometry (ICP-MS), noting that although GC-MS or HPLC-MS (with derivatisation) are typically used to analyse for alkylating agents; increased ppb sensitivity for sulfur and halogens attainable from modern ICP instruments makes this a viable approach for trace analysis of some alkylating agents, with or without derivatisation.[133] Dr Elder described various strategies used to limit[134] and detect mutagenic impurities in the pharmaceutical industry and noted that there are transferable learnings that may be valuable to those working in the analysis of chemical warfare agents (and their degradation products). In this regard, the pharmaceutical industry has a wealth of experience with trace analysis methods.[135]

14.3 In the subsequent discussion, the following point was raised:

Quantitative structure–activity relationship approaches to risk assessment in the pharmaceutical industry combine computational tools and the knowledge and experience of scientists, requiring multidisciplinary teams that include analytical chemists and toxicologists.

Subitem 14(b): Machine learning in chemical synthesis

14.4 Mr Marwin Segler (Westfälische Wilhelms-Universität Münster, Germany) provided a presentation on the use of machine learning to design chemical synthesis routes.[136] He described retrosynthesis, a tool used design synthetic routes, as a recursive transformation of target molecules into increasingly simpler precursors until arriving at a set of available starting materials. Despite the use of computer aided approaches

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132 For example derivatization strategies for GC/MS analysis, compare: (a) Direct derivatization and rapid GC-MS screening of nerve agent markers in aqueous samples; R. Subramaniam, C. Åstot, L. Juhlin, C. Nilsson, A. Östin; *Anal. Chem*; 2010, *82(17)*, 7452–7459; DOI: 10.1021/ac101604n. And (b) Development and validation of an automated static headspace gas chromatography-mass spectrometry (SHS-GC-MS) method for monitoring the formation of ethyl methane sulfonate from ethanol and methane sulfonic acid; K. Jacq, E. Delaney, A. Teasdale, S. Eyley, K. Taylor-Worth, A. Lipczynski, V. D. Reif, D. P. Elder, K. L. Facchine, S. Golec. R. S. Oestrichi, P. Sandra, F. David*; J. Pharm. Biomed. Anal.*; 2008, *48(5)*, 1339-1344. DOI: 10.1016/j.jpba.2008.09.028.

133 (a) Novel sensitive determination method for a genotoxic alkylating agent, 4-chloro-1-butanol in active pharmaceutical ingredients by LC-ICP-MS employing iodo derivatization; K. Harigaya, H. Yamada, K. Yaku, H. Nishi, J. Haginaka; *Anal. Sci.*, 2014, *30*, 377-382. (b) Sensitive quantitation of residual phenylhydrazine in antipyrine by LC-ICP-MS with iodo derivatization; K. Harigaya, H. Yamada, S. Horimoto, H. Nishi, J. Haginaka; *Anal. Sci.*, 2014, *30*, 845-850. (c) Recent advances in trace analysis of pharmaceutical genotoxic impurities; D. Q. Liu, M. Sun, A. S. Korda; *J. Pharm. Biomed. Anal.*, 2010, *51*, 999-1014. DOI: 10.1016/j.jpba.2009.11.009.

134 Analytical control of genotoxic impurities in the pazopanib hydrochloride manufacturing process; D, Q. Liu, T. K. Chen, M. A. McGuire, A. S. Kord*; J. Pharm. Biomed. Anal.*; 2009, *50(2),* 144-50. DOI: 10.1016/j.jpba.2009.04.002.

135 Analytical advances in pharmaceutical impurity profiling; R. Holm, D. Elder; *European Journal of Pharmaceutical Sciences*; 2015, *87*, 118-135. DOI: 10.1016/j.ejps.2015.12.007.

136 (a) Modelling chemical reasoning to predict and invent reactions; M. H. S. Segler, M. P. Waller; *ChemPubSoc Europe*; 2017, *23(25),* 6118-6128. DOI: 10.1002/chem.201604556. (b) Generating focussed molecule libraries for drug discovery with recurrent neural networks; M. H. S. Segler, T. Kogej, C. Tyrchan, M. P. Waller; available as a pre-print; 2017. arXiv:1701.01329. (c) Towards "AlphaChem": chemical synthesis planning with tree search and deep neural network policies; M. Segler, M. Preuß, M. P. Waller; available as a pre-print, 2017, arXiv:1702.00020.

to retrosynthetic analysis being 60 years old, current approaches tend to be slow and provide unsatisfactory results.

14.5 Mr Segler is developing Monte Carlo Tree Search (MCTS) methods as a tool to more efficiently find retrosynthetic routes.[137] His work has involved developing "policies" (rules) that guide the computational searching with filters to pre-select the most promising chemical transformations. To achieve this, deep neural networks were trained with 12 million reactions (effectively all the published organic chemistry reactions through 2014) and two sets of rules developed; 17,134 rules for the atoms and bonds changed in the course of a reaction, for both the reaction centre and the first degree neighbouring atoms; and an expanded set of 301,671 rules based on the reaction centre. Mr Segler reported that his system can solve retrosynthetic steps for nearly twice the number of molecules and is 30 times faster in comparison to search methods based on extracted rules and hand-coded heuristics.

14.6 The method has been able to generate retrosynthetic pathways that match routes reported in the literature (for compounds not included in the training set), however there are many limitations that must be overcome. These include the ability to find solutions for natural products, providing reaction conditions, predicting yields, stereochemistry, conformers, equilibria based reasoning, and inventing novel reactions.

14.7 In the subsequent discussion, the following points were raised:

(a) Machine learning has much potential for synthesis planning, ultimately promising the selection of better routes and conditions. Much progress is still needed before this potential can be fully realised.

(b) The goal to make chemistry "more predictable" was also a theme in the presentations on synthesis tools (Section 12). In this regard, including failed reactions and poor yield reactions in training sets may help strengthen rules and filters to provide better results (this has been demonstrated in machine learning tools for material science[138]).

(c) It has also been acknowledged that computational selection of synthetic planning and reaction conditions may have "dual-use" potential.

15. AGENDA ITEM FIFTEEN – Regulatory Frameworks

15.1 Dr Stephanie Dare-Doyen moderated the final presentation session of the workshop, focused on regulatory frameworks and their relevance to the implementation of the Convention.

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137 Learning to plan chemical syntheses; M. H. S. Segler, M. Preuss, M. P. Waller; available as a pre-print, 2017, arXiv:1708.04202v1.

138 Machine-learning-assisted materials discovery using failed experiments; P. Raccuglia, K. C. Elbert, P. D. F. Adler, C. Falk, M. B. Wenny, A. Mollo1, M. Zeller, S. A. Friedler, J. Schrier, A. J. Norquis; *Nature*; 2016, *533*,73-77. DOI: 10.1038/nature17439.

Subitem 15(a): Regulation in the chemical industry

15.2 Dr Becker-Arnold provided an overview of the variety of regulations, which include international conventions, and national and regional laws, that chemical industry is subjected to. These regulations cover areas of consumer and environmental protection, occupational health, chemical processes, transport and trade of chemical substances and products. In line with these multiple pieces of existing legislation, chemical industry is audited by regulatory agencies which oversee the enforcement of these laws. To follow the requirements, an Internal Compliance Programme within a chemical company's risk management processes must be implemented. Additionally, the chemical industry is committed to further voluntary initiatives improving its chemicals management and chemical processes.

15.3 Dr Becker-Arnold described requirements, industry implementation and the costs[139] associated with chemical and trade regulations. Her presentation focused on two examples: the Registration, Evaluation and Authorization and Restriction of Chemicals (REACh),[140] and the Convention. REACh, a chemical regulation, has been in place as a comprehensive system and legislative framework for chemical control in Europe since 2007. The Convention is the first and only disarmament treaty that outlaws the production, use and stockpiling of chemical weapons and their precursors, where national implementation requires registration and trade controls be put in place on the chemical industry.

15.4 In the subsequent discussion, the following points were raised:

(a) Regulations that reflect obligations to international conventions (are implemented through national policy implementation) that often follow different processes (with different compliance and reporting requirements) across different States Parties. From an industry view, a more harmonised approach would be beneficial and help the ability to comply effectively with the regulatory frameworks.

(b) In regard to costs, it was noted that the cost of registration of all chemicals under REACh for the EU is estimated at 5-10 billion Euro. Short term costs often arise with the implementation of new regulatory policies.

(c) REACh is about safe use of chemicals requiring risk assessments and mandatory data sharing. Dr Becker-Arnold noted that some substances are not actually covered by this specific regulatory framework (certain pesticides for example), however the precursors to such substances are.

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139 Cumulative Cost Assessment (CCA) for the EU Chemical Industry, European Commision, 2016. Available at: https://publications.europa.eu/en/publication-detail/-/publication/8eb1b47a-ee94-11e6-ad7c-01aa75ed71a1

140 For further information on REACh, see: https://echa.europa.eu/regulations/reach

Subitem 15(b): Biomediated processes and industry verification under the Chemical Weapons Convention

15.5 Ms Barbara Hedler discussed the issue of the meaning of the term "produced by synthesis" and presented the results of a survey[141] recently conducted by the OPCW to better understand how States Parties treat biomediated production processes in their implementation of the Convention.

15.6 Ms Hedler began by briefing the workshop on Part IX of the Verification Annex of the Convention,[142] which uses the term "produced by synthesis" as one of the requirements that makes a chemical production facility subject to declaration. Whether the term includes biochemical and biologically mediated processes ("biomediated processes") has been an outstanding issue on the agenda of the Executive Council of the OPCW since entry into force of the Convention in 1997. The SAB has made recommendations on the meaning, and are of the view that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis".[143] The SAB has considered the issue and made additional recommendations through reports from their TWGs on the Convergence of Chemistry and Biology[144,145] and Verification.[146]

15.7 The translation of the SAB's recommendation on the verification regime into policy continues to be discussed. Ms Hedler briefed the participants on a survey on biomediated processes recently conducted across States Parties. The survey results highlighted diverse views and practices across the States Parties in regard to declarations of other chemical production facilities (OCPFs).[147] Approximately 40% of the 32 States Parties[148] that responded, do, as a general policy, declare any plant site producing discrete organic chemicals (DOCs) regardless of the type of process

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141 Results of the Survey on Biomediated Processes (S/1534/2017, dated 14 September 2017). Available at: www.opcw.org/fileadmin/OPCW/S_series/2017/en/s-1534-2017_e_.pdf

142 Part IX of the Verification Annex to the *Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction*. www.opcw.org/chemical-weapons-convention/annexes/verification-annex/part-ix/

143 See paragraph 10 of: 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 (RC3-DG.1, dated 29 October 2012). Available at: www.opcw.org/fileadmin/OPCW/CSP/RC-3/en/rc3dg01_e_.pdf

144 See recommendations 18 and 19 of: Convergence of Chemistry and Biology: Report of the Scientific Advisory Board's Temporary Working Group (SAB/REP/1/14, dated June 2014). Available at: www.opcw.org/fileadmin/OPCW/SAB/en/TWG_Scientific_Advsiory_Group_Final_Report.pdf

145 A quick reference guide to the recommendations of the TWG on the Convergence of Chemistry and Biology is available at: www.opcw.org/fileadmin/OPCW/SAB/en/Convergence_of_Chemistry_and_Biology_1-01.pdf

146 See recommendations 9 and 10 of: Verification, Report of the Scientific Advisory Board's Temporary Working Group (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

147 OCPFs are defined in Part IX of the Verification Annex to the *Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction*. www.opcw.org/chemical-weapons-convention/annexes/verification-annex/part-ix/

148 Additional responses have been received since the original summary of results was published; an updated summary is forthcoming.

used in the facility (e.g. a biomediated or a traditional chemical process). Nevertheless, four States Parties indicated they exclude certain facilities such as those that produce alcoholic beverages and/or processes that utilise biochemical processes within living organisms, such as fermentation, from declaration. The States Parties that, as a general policy, do not declare plant sites producing certain DOCs, regardless of the type of process, also have divergent views and justifications for their approaches.

15.8 The response to the survey by States Parties indicated that, to implement the SAB's recommendation with the term "produced by synthesis" including biomediated processes, the largest potential impact on OCPF declarations would be for facilities producing ethanol (for alcoholic beverages and/or biofuels). This impact could be limited should exclusions be granted for DOCs used in food, beverages, and/or biofuels.

15.9 In the subsequent discussion, the following points were raised:

(a) The States Parties do not have a unified view of the meaning of "produced by synthesis". Resolution on this is being sought by the Industry Verification Branch through consultation with States Parties. The SAB believes it is important that policymakers reach a consensus view of the meaning, favouring or disfavouring the inclusion of biomediated processes. The SAB expressed its appreciation to those States parties who have engaged in these discussions.

(b) Could exemptions complicate the implementation of the Convention? A risk based approach might be used that takes into account what is relevant to the intent and purpose of the Convention.

(c) Confidentiality concerns by inspected parties are also noted, as there is significant innovation and intellectual property involved in the biotechnology sector.

16. AGENDA ITEM SIXTEEN – Thematic Discussions

16.1 Following the presentation sessions, the workshop participants engaged in interactive discussion to address key questions related to technological change and scientific advancements in the chemical industry and chemical production, and how these changes impact implementation of the Convention. Four topics were considered.

16.2 The first discussion was facilitated by Dr Jonathan Forman, addressing the topic of "advances in chemical production technologies and the synthesis of chemicals scheduled under the Chemical Weapons Convention".

(a) Participants were asked for their views on *what has changed and what impact might it have on recognising a relevant process?* And *if the answer changes when considering different production scales?* In regard to these questions, the following points were raised:

(i) Notable aspects of current industrial chemical production practices (across all sectors) include the adoption of automation and its ability to increase process control, integration of safety and regulatory

requirements into the design of production facilities, streamlined business practices (including the use of ERP systems), and the integration of big data and informatics into both chemical discovery and production processes.[149,150] These changes to industry over the past few decades can bring more visibility and transparency to the activities being undertaken at a production facility and can also result in more dedicated (less flexible) facilities.

(ii) Knowledge transfer and knowledge sharing amongst producers and developers is becoming an increasingly common requirement under regulatory frameworks covering chemicals and clinical studies involving chemicals.

(iii) Most participants were of the opinion that small scale, flexible and modular operating equipment provided greater opportunities for illicit or clandestine activities.

(b) The discussion provided the following conclusions:

(i) For verification purposes, up to date knowledge of processes and chemistry related to the schedules of the Convention is necessary for those conducting inspections. The increased transparency offered through modern practices in commercial production would still require appreciable levels of technical understanding to adequately make an assessment. Likewise, unusual practices even in small scale and less transparent production operations may not be recognised without adequate levels of knowledge (both explicit and tacit).

(ii) Questions were raised about the fitness of the Convention schedules to the object and purpose of the Convention given the changing global security environment. Views (in favour of and opposing), and procedures for updating the schedules to reflect current chemicals of concern that are not covered, were discussed.

16.3 The second discussion, facilitated by Mr Cheng Tang, addressed the topic of "advances in biological production technologies and the synthesis of bioregulators and/or biological toxins". Two questions were considered.

(a) *What is the current status of the chemical synthesis of bioregulators and/or biological toxins?* In regard to this question, the following points were raised:

(i) For bioregulators, the synthesis of small peptides can be performed in a cost-effective manner, but requires specialised equipment.

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149 (a) Big data analytics in chemical engineering; L. Chiang L1, B. Lu, I. Castillo; *Annu. Rev. Chem. Biomol. Eng.*, 2017, *8*, 63-85. DOI: 10.1146/annurev-chembioeng-060816-101555. (b) Demystifying industry 4.0: implications of internet of things and services for the chemical industry; R. Ravi, L.-C. Wu; MIT Research Report: MISI-2015-11; 2015. Available at: https://dspace.mit.edu/bitstream/handle/1721.1/102155/2015_11_Ravi_Wu.pdf?sequence=1.

150 (a) The drug plant of the future; R. Mullin; *Chem. Eng. News*; 2017, *95(21)*, 22-24. (b) Pharma partnership applies deep learning to very big data; R. Mullin; *Chem. Eng. News*; 2017, *95(4)*, 31-32.

(ii) Non-protein toxins (such as saxitoxin) often have complex molecular structures, making chemical synthesis impractical.[151,152] Isolation from their natural sources is a more likely route.

(iii) Synthesis of full length proteins by chemical methods is currently limited in its scalability with practical limitations on the production of protein toxins. Protein production technologies can produce protein toxins; however process development requires appropriate resources and expertise, and the compatibility of altered genomes and/or toxin products in host cells (this would also hold true for modified microbe production of non-protein toxins).

(b) *Is there an impact to the Chemical Weapons Convention given the capabilities available for production of bioregulators and/or toxins?* In regard to this question, the following points were raised:

(i) 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 weaponisation is thought to be impractical.

(ii) Acquisition of such materials by Non-State Actors would likely be through natural sources rather than biotechnologies. If biotechnologies were to be used, it would be expected that they might entail the use of disposable equipment and operate on small scales.

(c) The discussion provided the following conclusions:

(i) A risk assessment 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.

(ii) As in the previous discussion, it was recognised that a review of the Convention's schedules may be of value in regard to any bioregulators and toxins that are determined to pose a risk to non-proliferation.

16.4 The third discussion was facilitated by Dr Christopher Timperley, addressing the topic of "new synthesis tools and technologies for enhancing the capabilities of the OPCW Designated Laboratories".

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151 Synthesis of the paralytic shellfish poisons (+)-gonyautoxin 2, (+)-gonyautoxin 3, and (+)-11,11-dihydroxysaxitoxin; J. V. Mulcahy, J. R. Walker, J. E. Merit, A. Whitehead, J. Du Bois; *J. Am. Chem. Soc.*, 2016, *138(18)*, 5994–6001. DOI: 10.1021/jacs.6b02343.

152 Chemistry's toughest total synthesis challenge put on hold by lack of funds; K. Krämer; *Chemistry World*, 15 January 2015; https://www.chemistryworld.com/news/chemistrys-toughest-total-synthesis-challenge-put-on-hold-by-lack-of-funds/8152.article

(a) Participants were asked for their views on *what synthetic tools and methods are available for enhancing the capabilities of OPCW Designated Labs?* And *which synthetic technologies being adopted in academia and/or industry could benefit the Designated Labs?* In regard to these questions, the following points were raised:

(i) Flow reactors can produce small quantities of chemical warfare agents and their derivatives on demand and are potentially useful for synthesising analytical standards. However, flow reactors can also have disadvantages (including leakage and potential blockage by solid materials that precipitate during the course of a reaction), as these issues can impact safety, which is one of the main concerns during the synthesis of toxic chemicals in OPCW Designated Laboratories, tolerances of the system would need to be understood and procedures appropriately adapted.

(ii) Flow reactors can be coupled to analytical instruments, allowing for the compounds, once produced, to be immediately analysed and consumed (e.g. no need to isolate the materials with safe neutralisation of them immediately after analysis). This capability could be combined with combinatorial synthetic methods involving C1 to C10 alcohol precursors to generate sets of structures of nerve agents that are covered under the schedules of the Convention, for the purpose of collecting large volumes of analytical data in a short time under controlled conditions. It was also noted that with the range of reactivity shown by C1 to C10 alcohols, the methods for product synthesis may not be uniform across all such precursors, requiring appropriate levels of flexibility in the operating conditions of a flow system depending on the types of alcohol selected for such experiments.

(iii) Alternatively flow reactors could be used to produce amounts of chemical agent(s) for real-time environmental fate or toxicity studies under different conditions; possibly including microfluidic devices and chip based screening methods.[153] See also paragraph 12.6(c).

16.5 The fourth discussion was facilitated by Dr Stephanie Dare-Doyen, addressing the topic of "the impact of current trends and future directions in chemical production on the Chemical Weapons Convention verification regime". Two questions were discussed.

(a) *Which current trends and potential future directions in chemical production would be of concern for the Convention?* In regard to this question, the following points were raised:

[153] (a) Microfluidics-to-mass spectrometry: a review of coupling methods and applications; X. Wang, L. Yi; N. Mukhitov, A. M. Schrell, R. Dhumpa, M. G. Roper; *Journal of Chromatography A*, 2015, *1382*, 98-116. DOI: 10.1016/j.chroma.2014.10.039. (b) Recent advances in microfluidics combined with mass spectrometry: technologies and applications; D. Gao, H. Liu, Y. Jiang, J.-M. Lin; *Lab Chip*, 2013, *13*, 3309-3322. DOI: 10.1039/C3LC50449B.

(i) The diversity of fields of science relevant to both the Chemical and Biological Weapons Conventions is growing, and the distinction between "produced by synthesis" for chemicals and biologicals is blurring as a result of scientific disciplinary convergence and increased adoption by industry of biobased methods.

(ii) Inspections often focus on classical batch-scale manufacture. Continuous manufacture 24/7 often achieves the same capacity but the footprint of the production reactor is much smaller. However the chemical precursors and final products still need to be stocked.

(iii) It is becoming easier to manufacture toxic chemicals, using flexible, and in some cases disposable, production equipment. This raised a question on how the Convention would address mobile toxic chemical production facilities.

(iv) More general concerns were raised in regard to inconsistencies in policies and regulations across States Parties, the ability to understand a changing risk and security environment, and the failure to recognise opportunities from scientific advances for the implementation of the Convention (e.g. the failure to maintain adequate science literacy).

(b) *In light of advances in science and technology, and a changing security environment, are revisions to the verification approach necessary?* In regard to this question, the following points were raised:

(i) The points made in the earlier session on the verification regime (paragraphs 6.4-6.7) on risk-assessment based strategies for verification, revisiting on-site inspection procedures to focus on toxic chemicals with significant risk of misuse, and the possibility of using equipment with enabling capabilities for recognising chemicals of concern were reiterated.

(ii) In regard to risk assessment approaches to verification, the knowledge sharing and knowledge transfer seen across the chemical industry may provide access to useful inputs.

(iii) Review of the Convention's schedules in light of high risk chemicals was also discussed. It was noted that the general purpose criteria of Article II[154] would cover any chemical should it be used in violation of the Convention; however, for routine inspections unscheduled chemicals, even those with elevated risk for misuse, would not be considered.

(iv) Common across the four discussions of agenda item 16, is a need for operational knowledge of chemical (and biological) production

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154 Article II of the *Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction.* www.opcw.org/chemical-weapons-convention/articles/article-ii-definitions-and-criteria/

methods (including the synthesis and analysis aspects). Recognising unusual processes or modules within processes that are inconsistent with the allowable activities under the Convention is valuable in the face of technological change – for both prevention and post-event fact finding. Training exercises and proficiency testing could usefully take this into consideration.

(v) It was recognised that clandestine activities by their very nature will never be 100% preventable, while regulated commercial activities are more likely to continue becoming more transparent with the technologies being adopted for larger scale production, as per the discussion in paragraph 16.2(a).

(vi) Maintaining confidence amongst the States Parties is at the heart of the verification regime. In this regard, action by States Parties that seek to better understand scientific and technological change, enable knowledge sharing and demonstrate transparency were identified as opportunities that would support the verification regime.

17. AGENDA ITEM SEVENTEEN – Closure of the Workshop

The Chairperson closed the workshop at 13:15 on 5 October 2017.

18. AGENDA ITEM EIGHTEEN – Adoption of the Report

The drafting committee considered and adopted the report of the International Workshop on "Trends in Chemical Production".

ACKNOWLEDGEMENT

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Annex: List of Participants at the International Workshop on Trends in Chemical Production

Annex

LIST OF PARTICIPANTS AT THE INTERNATIONAL WORKSHOP ON TRENDS IN CHEMICAL PRODUCTION

	Participant	Institution
1.	Dr Pål Aas*	Norwegian Defence Research Establishment (FFI), Kjeller, Norway
2.	Professor Isel Pascual Alonso*	University of Havana, Cuba
3.	Professor Roberto Martínez- Álvarez	Complutense University, Madrid, Spain
4.	Mr Mario Antonić	State Secretary of the Ministry of Economy, Entrepreneurship and Crafts of Croatia
5.	Dr Tony Bastock	Contract Chemicals Ltd, United Kingdom of Great Britain and Northern Ireland
6.	Dr Renate Becker-Arnold*	BASF, Ludwigshafen, Germany
7.	Dr Andreas Beyeler	F. Hoffmann-La Roche AG, Switzerland
8.	Ms Andrea Božić	Saponia d.d., Osijek, Croatia
9.	Dr Olaf Burkhardt	Evonik Industries AG, Germany
10.	Professor Fabrizio Cavani	University of Bologna, Italy
11.	Dr Christophe Curty*	Spiez Laboratory, Switzerland
12.	Dr Stephanie Dare-Doyen	Organisation for the Prohibition of Chemical Weapons, The Hague, the Netherlands
13.	Dr David Elder	CMC Consultant, United Kingdom of Great Britain and Northern Ireland
14.	Ms Renata Florjanić	Croatian Chamber of Economy
15.	Dr Jonathan Forman[+]	Organisation for the Prohibition of Chemical Weapons, The Hague, the Netherlands
16.	Dr Kerry Gilmore	Max Planck Institute of Colloids and Interfaces, Potsdam, Germany
17.	Ms Barbara Hedler	Organisation for the Prohibition of Chemical Weapons, The Hague, the Netherlands
18.	Dr Zrinka Kovarik*[+]	Institute of Medical Research and Occupational Health, Zagreb, Croatia
19.	Dr Devin Leake	Ginkgo Bioworks, Boston, Massachusetts, United States of America
20.	Dr Nikolina Maček Hrvat	Institute of Medical Research and Occupational Health, Zagreb, Croatia
21.	Dr Detlef Maennig	International Council of Chemical Associations (ICCA)
22.	Ms Mirna Maravić[+]	Ministry of Economy, Entrepreneurship and Crafts of Croatia
23.	Dr Ernest Meštrović	Teva Group, Croatia
24.	Dr Ir. Nico Oosterhuis	Celltainer Biotech BV, Winterswijk Brinkheurne, the Netherlands
25.	Professor Zvonko Orehovec	University of Applied Science, Zagreb, Croatia
26.	Ms Gordana Pehnec Pavlović	Croatian Chamber of Economy

	Participant	Institution
27.	Ms Marlene Payva+	Organisation for the Prohibition of Chemical Weapons, The Hague, the Netherlands
28.	Dr Syed Raza*	Institute of Pesticide Formulation Technology (IPFT), India
29.	Mr Marwin Segler	Westfälische Wilhelms-Universität Münster, Germany
30.	Dr Sean Simpson	LanzaTech, Skokie, Illinois, United States of America
31.	Dr Koji Takeuchi*	National Institute of Advanced Industrial Science and Technology (AIST), Japan
32.	Mr Cheng Tang*+[155]	Office for the Disposal of Japanese Abandoned Chemical Weapons, Ministry of National Defence, China
33.	Dr Christopher Timperley*+[156]	Defence Science and Technology Laboratory (Dstl), Porton Down, United Kingdom of Great Britain and Northern Ireland
34.	Professor Ferruccio Trifirò*	Department of Industrial Chemistry, University of Bologna, Italy
35.	Dr René van Sloten	European Chemical Industry Council (cefic), Belgium
36.	Professor Richard Whitby	University of Southampton, United Kingdom of Great Britain and Northern Ireland
37.	Dr Florian Wurm	ExcellGene SA, Monthey, Switzerland
38.	Ms Tamara Zorbaz	Institute of Medical Research and Occupational Health, Zagreb, Croatia

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