OPCW

Scientific Advisory Board

Twentieth Session
10 – 14 June 2013

SAB-20/WP.3
11 April 2013
ENGLISH only

REPORT OF THE THIRD MEETING OF THE SCIENTIFIC ADVISORY BOARD TEMPORARY WORKING GROUP ON THE CONVERGENCE OF CHEMISTRY AND BIOLOGY

1. The Report of the Third Meeting of the Scientific Advisory Board (SAB) Temporary Working Group on the Convergence of Chemistry and Biology is hereby circulated to States Parties. The meeting was held in The Hague from 3 to 4 April 2013.

2. The Chairman of the SAB and the Director-General have agreed that this report can be circulated to States Parties in advance of the Twentieth Session of the SAB.

3. In accordance with the Rules of Procedure of the SAB, this report and the recommendations contained therein will be reviewed in detail by the SAB at its Twentieth Session.

Annex:

Report of the Third Meeting of the SAB Temporary Working Group on the Convergence of Chemistry and Biology

CS-2013-7776(E) distributed 11/04/2013

Annex

REPORT OF THE THIRD MEETING OF THE SAB TEMPORARY WORKING GROUP ON THE CONVERGENCE OF CHEMISTRY AND BIOLOGY

1. AGENDA ITEM ONE – Opening of the meeting and adoption of the agenda

1.1 The Scientific Advisory Board (SAB) Temporary Working Group (TWG) on the Convergence of Chemistry and Biology held its third meeting on 3 to 4 April 2013 at OPCW Headquarters in The Hague.

1.2 The meeting was chaired by William Kane on behalf of the SAB.

1.3 The meeting began with a tour de table to introduce the members of the TWG and invited guest speakers. The list of participants is given in the Appendix.

1.4 The following agenda was adopted:

(i) Opening of the meeting and adoption of the agenda;

(ii) Biologically mediated synthesis of chemicals.

(iii) Whether any biotechnological processes exist, other than biologically mediated synthesis, that are of relevance to the implementation of the CWC.

(iv) The meaning of "produced by synthesis".

(v) Whether there are other scientific disciplines, apart from biology, that are converging in a significant way with chemistry.

(vi) The potential benefits to the CWC of the convergence of chemistry and biology.

(vii) Any other business, and

(viii) Recommendations, intersessional work, adoption of the TWG report from the meeting, and date of the next meeting.

2. AGENDA ITEM TWO – Biologically mediated synthesis of chemicals

2.1 Robert Mathews provided his perspective on the CWC negotiating history of the term "biologically mediated processes". The speaker recalled that in 1992, there was lack of agreement as to whether the OCPF regime should be limited to 'purely chemical production processes' (i.e. where all reactants, catalysts, etc. were chemicals) or whether chemical production processes containing a 'biological element' (e.g. bio-mass feedstock, biological catalyst, fermentation process, etc.) should also be included. This issue could not be resolved by the Geneva negotiators so in order to obtain an agreed Convention text which could be endorsed by the UN General Assembly, a 'creative ambiguity' was inserted in the Convention Text in Part IX Paragraph 1 with the term "produced by synthesis". This term was interpreted as

chemical production without any biological element by those wanting to exclude "biological production" of chemicals, and to include production processes containing a 'biological element' (e.g. biosynthesis) by those who wanted biological production included in the OCPF regime. The presentation concluded with the question: What is the term most commonly used by industry in 2013 when referring to chemical production processes which contain a 'biological element'?

2.2 The speaker recalled that in the OPCW Preparatory Commission, the term "biologically mediated process" was developed in an unsuccessful attempt to resolve the "production by synthesis". He noted that the term "biologically mediated process" is not used in the Convention and was never defined by the Preparatory Commission.

2.3 **Action**: In discussion, the TWG suggested a different term that could capture all relevant biological processes used in production of chemicals would be useful. All TWG members were requested to give this some thought in advance of the next meeting.

2.4 In following up recommendations from the first two TWG meetings, Professor Scott Mohr (Boston University, guest speaker) presented an overview of bioregulators and toxins as potential bioweapons, pointing out their utility for limited-scale attacks, but unlikely use in major operations. He then gave a summary of the potential of synthetic biology and de novo enzyme engineering (as exemplified, for example, by the work of Professor David Baker's group at the University of Washington) to create novel, powerful and difficult-to-detect bioweapons, including a modified version of anthrax that could be extremely potent. He also observed that sophisticated new DNA sequence-analysis tools (in particular Professor Evan Johnson's new tool "Pathoscope") should prove valuable in identifying disguised, pathogenic organisms.

2.5 In discussion, the following points were made:

(a) **Action**: The TWG proposed to invite a speaker with expertise in drug delivery technology, especially in regards to aerosolisation, formulation, avoiding host defences, and targeting, to further explore the risk of weaponisation of bioregulators.

(b) Large scale production of toxins could be easier with engineered organisms.

(c) Use of synthetic biology to engineer safety into a microbial "chassis" was noted. However, such developments were moving forward slowly.

2.6 Hua Li presented information on the application of biologically mediated production to the synthesis/production of ricin (a Schedule 1A chemical). Key points were:

(a) Awareness and concerns about ricin have been growing in the past decade as the result of increased incidents of attempted ricin poisoning and terrorism-related activities.

(b) Recent research is mainly focused on ricin toxicity, detection, countermeasures and its medical applications (e.g. immunotoxins used for cancer therapy).

(c) Castor beans are still the main source of crude and pure ricin, and the extraction and purification processes are relatively easy and cheap.

(d) Ricin, A-chain, B-chain and their analogues can be produced by biologically mediated synthesis.

(e) Recently, a draft genome sequence of the ricin producing oilseed castor bean was published. This may enable metabolic engineering to obtain safe sources for improving castor oil production in crop plants lacking ricin. It may also have implications on biologically mediated process for ricin production.

2.7 **Action**: The TWG concurred with the presentation. Evidently, ricin research is a representative model for production of protein toxins using biologically mediated methods and provides further insight into advances in countermeasures and detection. Hua Li agreed to follow relevant developments and report to the TWG at the next meeting.

2.8 Piers Millet summarized an article on a synthetic ribosome to highlight the rapid progress where simple designed molecules perform tasks similar to those of biological components.[1] The authors claim a molecular machine could replace the need for engineered organisms for the synthesis of peptides and other biological materials.

2.9 In discussion, the following points were made:

(a) These reports provide strong examples of why it is important to further explore the convergence of chemistry and biology.

(b) Use of the topological capacity of DNA to engineer novel molecular shapes has potential convergence with nanotechnology.

2.10 Dr. Joel Cherry (President of R&D, Amyris Biotechnologies; guest speaker) presented an overview of Amyris Biotechnologies. The company had started out with a research project to synthesize the anti malaria drug artemisinin through metabolic pathway engineering of yeast cells. Based on the results of that research, the company has developed an industrial biology platform that synthesises a range of organic chemicals that are found in a variety of consumer products including fuels, lubricants, home and personal care products, polymers and plastic additives, flavors and fragrances, and cosmetics. The company produces for example squalane, an important ingredient for cosmetics that generally has been extracted from deep water shark liver oil. The company produced engineered yeast cells utilizing, among other techniques, random mutagenesis. As a result of this, using sugar as a feedstock, branched unsaturated hydrocarbons can be produced on an industrial scale in very large fermenters with volumes in excess of hundred thousand litres.

[1] B. Lewandowski et al, *Science*, 11 January 2013, Vol. 339 no. 6116 pp. 189-193; see also J. Wang, B. Feringa, *Science*, 18 March 2011, Vol. 331 no. 6023 pp. 1429-1432.

2.11 The TWG noted the following points from the presentation:

(a) The presentation provided insight into what was required to work with an engineered yeast-strain production process from laboratory research to pilot plant and scale-up to commercial operation.

(b) Significant investment and time are required to build the technical platform to go from microliter plate screening of yeast-strain candidates to commercially meaningful production of materials.

(c) The application of microfluidics and increased use of automation have begun to improve the turn around time for the identification of scale-up candidates.

(d) Yeast was noted as the preferred chassis over E. coli for the Amyris product line; benefits are post-translational modification, homologous recombination, and less toxic waste disposal.

(e) All fermenter-based production sites have potential, with appropriate DNA input into the chassis organism, to produce toxins. Screening at the point of DNA synthesis could be the best way to monitor.

(f) The presentation demonstrated how mature the methods and techniques have become and that large numbers of complex chemicals can be produced on a commercial scale by engineered organisms.

(g) The TWG noted that Amyris was originally founded by three post-doctoral fellows in 2003. Ten years later the company is developing and producing chemicals for a broad range of consumer products using a synthetic biology platform on an industrial scale.

2.12 **Action**: Having considered and discussed the five presentations, the TWG thought it would be useful to invite guest speakers on the design of enzymes, and the use of engineered plants to produce vaccines (which could be useful in the context of the TWG's deliberation on countermeasures).

2.13 **Action**: Furthermore, Scott Mohr agreed to prepare a brief background note on the design of enzymes and Bill Provine offered to update the group on the enzymes produced by DuPont. Piers Millet agreed to provide a briefing on the use of engineered DNA scaffolds to improve catalytic efficiency.

2.14 The TWG noted that biotechnology industry-led security concerns are being addressed through a raft of complementary measures including screening of conventional gene synthesis orders and community engagement.

3. AGENDA ITEM THREE – Whether any biotechnological processes exist, other than biologically mediated synthesis, that are of relevance to the implementation of the CWC

3.1 William Kane recalled from the previous meeting that the purpose of this agenda item is to make sure the TWG considers all chemical production processes using biological methods.

3.2 In discussion the following points were made:

(a) From the discussion under Agenda Item 2, the TWG now understood this term of reference to mean "what are the applications of life sciences relative to the CWC?" and would further explore the topic along this line.

(b) **Action**: Each TWG member agreed to forward to the TWG chair and secretary any relevant novel examples of convergence reported in the scientific literature, for review by the TWG. The TWG secretary would post these articles on the TWG portal.

4. AGENDA ITEM FOUR – The meaning of "produced by synthesis"

4.1 Stefan Mogl recalled in a presentation that the TWG in its last meeting had recommended that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis" (VA.IX.1a), and that the SAB had endorsed this recommendation (SAB-19/1 and RC-3/DG.1). He emphasized that if this recommendation was to be implemented, a discussion should be held on what technical guidance the TWG could provide to assist the identification of relevant facilities that are employing biological and biologically mediated processes, and which may be considered relevant to the CWC in the future.

4.2 The discussion that followed emphasized that there has been a significant increase in the production of chemicals through biological and biologically mediated processes. The TWG agreed that there were a number of factors to be considered, some applying to this TWG and others more to the TWG on Verification, which should also be consulted on the matter. The group agreed that for the next meeting, all members should prepare themselves for a technical discussion on the potential implications that this development may have for implementation of Part IX of the Verification Annex.

4.3 In discussion, the following points were made:

(a) **Action**: Robin Black and Stefan Mogl agreed to brief the convergence TWG on the relevant outcomes from the verification TWG meeting scheduled for September 2013.

(b) **Action**: Commentators claim that by the year 2020, 10% of the volume of all chemical products will be produced by biological or biologically mediated processes. The TWG acknowledged that technical aspects of these changes will need to be addressed in a timely fashion.

5. AGENDA ITEM FIVE – Whether there are other scientific disciplines, apart from biology, that are converging in a significant way with chemistry

5.1 The TWG recalled that numerous scientific disciplines, e.g. engineering, mathematics, physics, materials science, computer science, and informatics were enabling the convergence of chemistry and biology. In discussion, the following points were made:

(a) The TWG understood this term of reference to cover developments in other scientific disciplines and technologies that are relevant to CWC.

(b) **Action**: The TWG considered that bioregulators presently pose a low risk for use as a chemical weapon. However, since nanopackaging/delivery could change this view; Djafer Benachour agreed to look into this aspect during the intersessional period.

(c) **Action**: Piers Millet agreed to draw on the work done in the BWC context on monitoring enabling technologies and to brief the TWG further.

(d) **Action**: Robin Black agreed to look into biosensors during the intersessional period.

(e) **Action**: Scott Mohr agreed to look into the extent to which informatics is converging with chemistry.

6. AGENDA ITEM SIX – The potential benefits to the CWC of the convergence of chemistry and biology

6.1 Mahdi Balali-Mood presented a comprehensive overview of medical treatments against nerve agents and presented clinical data on victims of sulfur mustard exposure in the Iran-Iraq war. The speaker noted that benefits in treatments for sulfur mustard are mostly supportive and symptomatic.

6.2 Robin Black presented an overview of advances in detection, focused on Schedule 1 chemicals, mostly on nerve agents. Although the majority of fielded chemical warfare agent (CWA) detectors rely on physicochemical principles, CWA detectors with biological sensing elements have been in service for more than 40 years. The most widespread examples are the use of the enzymes acetylcholinesterase and butyrylcholinesterase for the detection of organophosphorus nerve agents. These enzymes have been used in automated vapour detectors, wet chemistry kits, tickets and Dräger-type tubes, and provide very sensitive devices for detecting nerve agents. More recently a contamination disclosure spray based on cholinesterase has been commercialised. Most of the recent developments employing biological sensing elements have concerned prototype biosensor diagnostic devices for nerve agent exposure. These have been based mainly on measuring active cholinesterase in blood, some including a reactivation stage to overcome the problem of uncertain baseline levels of enzyme. Biosensors based on the enzyme OP hydrolase have also been reported, as have a limited number of immunoassays. Future developments are likely to include improved enzymes and antibodies, and further exploitation of

nanotechnology. Bioassays have generally been the norm for initial detection of saxitoxin and ricin, and have benefitted from recent technological advances.

6.3 In discussion, the following points were made:

(a) The TWG noted that it is unlikely that detectors with biological sensing can meet all requirements for field CW agent detectors for the foreseeable future.

(b) Higher affinity antibodies and engineered enzymes would be needed for improvements.

(c) **Action**: Phillip Coleman agreed to inform the group about advances in portable mass spectrometers at the next TWG meeting.

6.4 Robert Mathews presented an overview of developments in physical protective equipment and the effect of convergence and nanotechnology on current and future approaches. He noted that current research is directed at enhanced protection and more user friendly materials that provide reduced physiological burden and are less cumbersome. He also noted research efforts to develop self decontaminating protective clothing (incorporation of enzyme and/or catalysts).

6.5 In discussion, the following points were made:

(a) The TWG noted that it is difficult to improve on carbon as a filter material, due to its adsorbent properties and relatively low cost. Layers of carbon cloth and fibres are very promising as a way to keep adsorption properties and make more user friendly filters.

(b) The TWG noted that aerosol protection is currently lacking in much of the available protective gear.

(c) Noting that companies producing protective equipment are currently supplying first responders (fire, police, hazardous material clean up crews, etc), the TWG suggested to broaden the scope of it's monitoring of protective equipment to include first responders.

(d) **Action**: The 11th International Symposium On Protection Against Chemical And Biological Warfare Agents will be held in Stockholm in June 2013. Hua Li agreed to report back to the TWG on developments showcased at this exhibition.

6.6 Piers Millet presented some new developments in prion research.[2] In discussion, the TWG recommended to monitor such developments as the understanding of the way chemical changes in structure can impact biological function, could lead to improved countermeasures.

6.7 In discussion of the four presentations, the TWG noted that despite the rapid pace of advances and discoveries, commercial development has been slow. It was pointed out

[2] J. Bremer et al, *Nature Neuroscience*, 2010, Vol. 13. 310-318 .

that it is difficult to move from proof of concept under ideal laboratory conditions to rugged fieldable products.

7. AGENDA ITEM SEVEN – Any other business

7.1 Piers Millett reviewed a series of papers examining the use of Clustered Regularly Interspaced Palindromic Repeats (CRISPR) and CRISPR Associated System 9 (CAS9) for genome engineering as an example of an emerging enabling technology in the life sciences.[3] The CRISPR CAS9 system was identified in 2012 as the mechanism used by bacteria to incorporate into their genome, elements taken from viruses they have encountered. This was the mechanism enabling a previously identified rudimentary 'immune' system against viral infections and horizontal gene transfer. Papers published in February and March 2013 suggest that the CRISPR CAS9 system can be altered to enable cheap, flexible and fully customisable editing of DNA in humans, mice and yeast. Proponents of the system suggest that it might become a major enabling tool over the coming years.

8. AGENDA ITEM EIGHT – Conclusions, recommendations, plan of action for intersessional period, elaboration of the TWG report and date of the next meeting

8.1 Recommendations and action points for the intersessional period are recorded under the relevant agenda items: cf paragraphs 2.3, 2.5, 2.7, 2.12, 2.13, 3.2, 4.3, 5.1, 6.3, and 6.5.

8.2 The fourth meeting of the TWG was tentatively scheduled for 5-7 November, 2013.

8.3 Bearing in mind paragraph 5 of the terms of reference of the TWG, the TWG will produce a summary report of its findings and recommendations by the end of the two years, and forward this to the SAB and the Director-General for their review.

9. AGENDA ITEM NINE – Closure of the meeting

9.1 The Chairperson closed the meeting at 19:10 on 4 April 2013.

Appendix:

List of Members of, and Participants in, the Third Meeting of the Temporary Working Group on the Convergence of Chemistry and Biology.

---

[3] R. Barrangou, *Science*, 23 March 2007, Vol. 315, pp. 1709-1712; E. Deltcheva, *Nature*, 31 March 2011, Vol. 471 pp 602-607; A. Al-Attar, et al, *Biological Chemistry*. Vol. 392, Issue 4, Pages 277-289; P. Mali, et al, *Science*, 15 February 2013, Vol. 337, pp. 823-826; M. Jinek, et al, *Science*, 17 August 2012, Vol. 337, pp. 816-821; L. Cong, et al, *Science*, 15 February 2013, Vol. 337, pp. 819-823.

Appendix

LIST OF MEMBERS OF, AND PARTICIPANTS IN, THE THIRD MEETING OF THE TEMPORARY WORKING GROUP ON THE CONVERGENCE OF CHEMISTRY AND BIOLOGY
THE HAGUE, THE NETHERLANDS
3 – 4 APRIL 2013

Participant	Institution
Professor Mahdi Balali-Mood	Medical Toxicology Centre, Imam Reza Hospital, University of Medical Sciences, Mashhad, Islamic Republic of Iran
Professor Djafer Benachour*	Ferhat Abbas University, Ministry of Higher Education and Scientific Research, Setif, Algeria
Dr Robin Black	Defence Science and Technology Laboratory (DSTL), Porton Down, United Kingdom of Great Britain and Northern Ireland
Dr Philip Coleman	ECM Technology (Pty) Ltd, Pretoria, South Africa
Professor Roderick Flower	William Harvey Research Institute at Barts and the London School of Medicine and Dentistry, United Kingdom of Great Britain and Northern Ireland
Mr William Kane[4]*	Consultant of Monsanto Company, United States of America
Professor Hua Li	Chinese Academy of Military Medical Sciences, China
Dr Robert Mathews	Defence Science and Technology Organisation, Melbourne, Australia
Dr Piers D. Millet	United Nations, Switzerland
Mr Stefan Mogl*	Spiez Laboratory, Switzerland
Dr William D. Provine [5]	DuPont Central Research & Development, United States of America
Professor Igor Rybalchenko*	Military Science Centre of the Ministry of Defence, Moscow, Russian Federation
Dr Muhammad Zafar-Uz-Zaman*	National Engineering and Scientific Commission (NESCOM), Islamabad, Pakistan
Dr Joel Cherry (guest speaker)	Amyris Biotechnologies, Emeryville, United States of America
Professor Scott Mohr (guest speaker)	Bioinformatics Graduate Program and the Department of Chemistry, Boston University, United States of America

* Member of the Scientific Advisory Board.

- - - o - - -

4 Chairman of the TWG on the Convergence of Chemistry and Biology.

5 Attended by teleconference on the first day and the second half of the second day.