CONVERGENCE OF CHEMISTRY AND BIOLOGY

REPORT OF THE SCIENTIFIC ADVISORY BOARD'S TEMPORARY WORKING GROUP

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Convergence of Chemistry and Biology

Report of the Scientific Advisory Board's Temporary Working Group

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Organisation for the Prohibition of Chemical Weapons

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Executive Summary

Bulk and fine chemicals are being produced increasingly using biologically mediated processes, e.g. by microbial fermentation or using enzymes as catalysts. It is estimated that approximately 10% of chemical production volume will use such processes by 2020.[1] This trend is being driven by commercial and environmental factors, and particularly by competition for conventional feedstocks.

Key enabling technologies have resulted in a rapidly expanding capability to redesign or manipulate organisms for specific purposes, and the ability to design and engineer improved enzymes (such as through metabolic engineering, enzyme engineering, synthetic biology, or traditional recombinant DNA technology).

Although there are concerns that biotechnology could be applied to the production of new toxic chemicals, bioregulators and toxins, the temporary working group (TWG) assessed that potential applications to scheduled chemicals are currently limited. Scaling up a new biological process will continue to take a considerable investment of capital, resources and time; these considerations could reduce the likelihood of using such methods for large scale production of chemicals of concern, however, biomediated processes might still be effective for producing weaponisable quantities of toxins that are lethal to adult humans in microgram or lower dosage. It was also noted that similar concerns were raised in the early days of recombinant DNA technology.

In parallel to biotechnological innovation, substantial advances have been made in the chemical synthesis of molecules of biological origin. Commercial DNA synthesis has advanced to the point where whole genomes (an organism's total genetic material) can be synthesised and compiled, and viruses, including influenza[2] and coronavirus[3], have been reconstructed. Parallel research has enabled the rational engineering of viral capsids.[4]

Advances in the semi-automated synthesis of peptides have enhanced the ability to synthesise bioregulatory chemicals that mediate functioning of the body and other peptides with high physiological activity. Increased sophistication in organic chemistry has enabled the chemical synthesis of increasingly more complex biological molecules, including toxins, although generally on a scale that poses no threat to the purposes of the Convention.

Enabling technologies have been, and will remain, critical factors affecting the pace of change and convergence in the life sciences. Key technologies contributing to, and benefitting from the convergence of chemistry and biology, include: DNA sequencing and synthesis, informatics, computing capacity, availability and sharing of technical data on the Internet, and automated robotics in research and development (R&D).

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[1] "Biomass chemicals to be competitive in 10-15 years", *ICIS Chemical Business*, April 2-15, 2012 edition, page 24.
[2] R. Wang, J. K. Taubenberger, *J. Virol*., 2014, 88, 1815-1818.
[3] B. Rockx, et al, *J. Virol*., 2007, **81**, 7410-7423.
[4] C. Porto, et al; *PLOS Pathog*, 2013, **9(3)**: e1003255. doi:10.1371/journal.ppat.1003255.

Multidisciplinary research teams are becoming the norm, encompassing a range of technical expertise, including chemistry, biology, physics, computing, engineering, materials science and nanotechnology.

The increasing use of biologically mediated production processes has implications for the Chemical Weapons Convention verification regime. The temporary working group has reviewed the meaning of the term 'produced by synthesis' as it applies to Part IX of the Verification Annex of the Convention, in the context of declarations required for OCPFs (Other Chemical Production Facilities). The view of the TWG was that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis". Many facilities taking advantage of biologically mediated production processes, however, may not be relevant to Part IX of the Verification Annex and a detailed set of exemptions may be scientifically justified (such as facilities producing alcoholic beverages or biofuels).

New production processes, combined with developments in drug discovery and delivery, could be exploited in the development of new toxic chemicals that could be used as weapons. Such developments would still be covered by what is known as the 'general purpose criterion', but this highlights the importance of monitoring developments in science and technology.

Convergence is increasing the overlap between the remits of the Chemical Weapons Convention (CWC) and Biological Weapons Convention (BWC), historically restricted mainly to bioregulators and toxins. This will require increasing the interaction between CWC and BWC technical experts.

The TWG considered other areas of science and engineering impacting on developments in chemistry and biology. In particular, nanotechnology is playing an important role in improving drug delivery to the body, and in the development of biosensors.

The convergence of chemistry and biology is providing major benefits to humankind, particularly in health care, alternative energy sources, and in environmental control. Combined with other advances, particularly in nanotechnology, it is also being exploited in developing improved defensive countermeasures against chemical and biological warfare agents that will have implications for verification, and assistance and protection against weapons. There have been beneficial developments in protective clothing and equipment, decontamination, verification, detection/diagnostics, and medical countermeasures.

Recommendations to the Director-General

The TWG made 19 recommendations (see Section 3 starting on page 23). The key recommendations are in summary:

- The SAB and the TS should continue to monitor advances and trends in production technologies relevant to convergence, and assess the relevance of

these processes to verification under the CWC. Regular engagement with subject matter experts, e.g. from the biotechnology industry, will be required. See recommendations 1-4 and 18-19 from Section 3.

- Advances in systems and synthetic biology, which have enormous potential for beneficial and commercial purposes, should be monitored by the SAB and the TS, particularly in terms of enhancing the capability and capacity to synthesise more complex chemicals (in particular toxic chemicals, toxins and bioregulators). Regular engagement with subject matter experts will be required. See recommendations 2 and 5-6 from Section 3.

- Advances in nanotechnology, particularly as they apply to improved defensive countermeasures against CW, should be monitored. See recommendations 9 and 11 from Section 3.

- As the convergence of chemistry, biology and other sciences is a technically complex area, consideration should be given to the development of outreach material to assist staff at States Parties permanent missions to the OPCW in understanding possible implications for the CWC. See recommendation 14 from Section 3.

- A structured approach to maintaining contacts with the BWC community should be established. Existing relationships should be further developed to bring together technical expertise in areas of common interest. See recommendations 15-17 from Section 3.

- With the rapid pace of advances, consideration should be given to re-activating the TWG on Convergence periodically, e.g. every 5 years prior to the SAB report to the Director-General on science and technology (S&T), in order to assess recent advances. See recommendations 12-13 from Section 3.

1. Objectives of the TWG on Convergence of Chemistry and Biology[5]

In the late 1980s, when the negotiators of the Chemical Weapons Convention (CWC) in Geneva were considering chemical production, they focused primarily on the chemical production processes that had been used for chemical warfare agents (mostly nerve and blister agents) and their precursors.[6] However, even at that time, a substantial number of chemicals were being commercially produced through 'biologically mediated processes'.[7]

In recent years, there has been increasing interest in how rapid advances in the life sciences (including the convergence of chemistry and biology) might affect implementation of the CWC. This has included recognition that some of these developments have the potential to be misused, for example, for the production of toxic chemicals, including toxins and bio-regulators, through biologically mediated processes. The implications for such use were considered at a meeting held jointly by the Organisation for the Prohibition of Chemical Weapons and the International Union of Pure and Applied Chemistry (OPCW/IUPAC) in Zagreb in 2007.[8] The outcomes of the Zagreb workshop were reflected in the Director-General's report to the CWC Second Review Conference in 2008.[9] The IUPAC workshop held at Spietz in February 2012, further highlighted the need to consider convergence of the sciences.[10]

Many of the articles published on implications for the CWC of rapid advances in the life sciences, including the convergence of chemistry and biology, have approached the topic from the perspective of what is theoretically possible. Few articles have discussed what is realistically possible to achieve with the current state of development of science and technology. Thus, the Director-General expressed the view that the convergence of chemistry and biology warrants further study at a more practical level, and that additional advice might be sought from the OPCW Scientific Advisory Board (SAB), from States Parties that have assessed these developments, and from stakeholders in industry and academia.[11]

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[5] From Chairs briefing to the TWG by R. J. Mathews at the First Meeting on 15 November 2011.
[6] See for example, R.J. Mathews, The Regime for Other Chemical Production Facilities: A Technical Perspective, Harvard-Sussex Program, CBW Bulletin, 2009, **83**, 5-13.
[7] M. K. Turner, 'Biological Catalysis and Biotechnology', Chapter 6 in 'The Chemical Industry' (Ed. C. A. Heaton), (Blackie, London, 1988).
[8] M. Balali-Mood et al; *Pure Appl. Chem*., 2008, **80**, 175-200.
[9] Note by the Director-General, Report of the Scientific Advisory Board on Developments in Science and Technology, (RC-2/DG.1, dated 28 February 2008), Paragraph 2.6; this paragraph is reproduced in footnote 11.
[10] www.opcw.org/index.php?eID=dam_frontend_push&docID=15319
[11] From RC-2/DG.1, dated 28 February 2008: "The growing convergence between chemistry and biology is an issue that may need further reflection. These trends clearly have an impact on the scientific basis of the Convention, but it is less clear at this stage how the implementation process should be adapted. An obvious aspect is the need to ensure that the implementation process, at both the national and the international level, is firmly based on the premise that all toxic chemicals and their precursors are chemical weapons unless they are intended for purposes not prohibited, and so long as their types and quantities correspond to such purposes. At the practical level, however, more study is required. While the further

There has also been increasing interest in the possible implications of rapid advances in science and technology on the BWC. This was reflected in the report of a workshop co-hosted by the US National Academy of Science and Chinese Academy of Science, held in Beijing in 2010.[12] Three main themes emerged from the Beijing workshop: *The pace of change* was accelerating due to advances in enabling technologies, such as high-speed computing and high-throughput screening; *Diffusion of knowledge* was being facilitated and supported by internet coverage and an effective global communications network; *Integration and convergence* is occurring because of a blurring of boundaries between sciences and the transfer of ideas and tools between disciplines.[13]

With the increasing convergence of chemistry and biology, several conclusions were of joint concern for both the BWC and CWC. While chemical weapons and biological weapons are covered by their respective conventions, both conventions include toxins and other 'mid-spectrum' agents in their remit; although the CWC Schedules refer specifically only to saxitoxin and ricin for verification purposes. With convergence there is increasing commonality of the science and technology that underpins the two treaties.

The OPCW Director-General requested the SAB, at its Sixteenth Session, to consider the implications for the CWC. In its report, the SAB recognised that "these developments could potentially be misused, for example, to produce toxic chemicals and toxins through biologically mediated processes", but "that it would be important to have access to expertise from the biotechnology industry to assist the SAB in completing an assessment. Accordingly, the SAB recommended the establishment of a temporary working group

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development of the OCPF verification regime, in principle, seems an appropriate direction in which to proceed, the differences between the design criteria underlying that regime and the characteristics of the facilities in industry and academia that are at the forefront of the cross-over between chemistry and biology need to be recognised. There are also legal issues arising, on the one hand, from the overlap between the regimes of the Convention and the Biological and Toxin Weapons Convention, and, on the other hand, from the regime differences between those two treaties. The Director-General is of the view that this matter warrants further study and that additional advice might be sought from the SAB, from States Parties that have assessed these developments, and from stakeholders in industry and academia. Such additional advice would facilitate the consideration of this issue by the policy-making organs in due course."

[12] Trends in Science & Technology Relevant to the BWC. Report of an International Workshop, held 31 October-3 November 2010, Beijing. Nat Academies Press, Washington DC. Available from: http://www.nap.edu/catalog/13113.html. The conference reviewed: *Developments in design, fabrication and production*, which included new bioinformatic and computational tools, systems biology, synthetic biology, the use of bioreactor and transgenic animal technology, transgenic plants and recombinant pharmaceuticals; *Developments in dispersal and delivery* technologies, including aerosol and aerobiology technology, nanostructured delivery systems for drugs, proteins and cells and targeted delivery systems; *Developments in detection, identification and monitoring,* utilising post-genomic technologies bio-forensics and emerging biosensors technologies; *Defense and countermeasures*, including vaccines and medical countermeasures, monitoring and molecular diagnosis of emerging infections, human, and animal, and concluding with an overview of how the Internet has changed scientific interchanges and the influence of technology on global scientific collaboration.

[13] Many of the topics addressed at the Beijing meeting had primary relevance to the BWC. Conclusions included: all future scientific and technical developments relevant to the BWC fall within what is known as the 'general purpose criterion'; developments impact all articles of the BWC; it is important to understand the trends and evaluate their effect on the BWC; the scientific community should engage to monitor and assess these developments. However, with the increasing convergence of chemistry and biology, several issues were of joint concern with the CWC.

(TWG) to further explore the convergence of chemistry and biology, and implications for the Convention.[14]

The Director-General established the TWG in 2011. To meet the objectives of the TWG, experts from a broad range of backgrounds that included industrial and academic scientists, defence laboratory scientists, toxicologists, analytical chemists and chemical engineers (including those with experience in biomediated processes) were appointed. The expertise of the TWG was complemented with guest speakers, whose experience covered commercial biotechnology, informatics, and DIY biology. The complete terms of reference (TOR) of the TWG and a list of TWG members (and guest speakers) can be found in Annexes 1 and 2 of this report.

Reports from each meeting of the TWG were submitted to the SAB and made available to the Director-General and the States Parties through the OPCW website.[15]

2. Findings of the TWG

The processes that are used in the biologically mediated synthesis of chemicals (TOR 3a i)

Fermentation Technology and Metabolic Engineering

One of the oldest biological processes is the traditional yeast fermentation of sugars (from carbohydrate containing plant material) to produce ethanol. This biological process continues to be used by the food and beverage industries for wine, beer, spirits production, and food preservation. It has also been adopted by the chemical and biotech industry to produce other chemicals as advances in biotechnology, such as metabolic engineering, have been realised.

Metabolic engineering is a key technology being employed increasingly by industry. It is defined as the targeted and purposeful alteration (using genetic engineering techniques) of an organism's biochemical processes in order to better understand how the pathways work, or to redesign them to produce a different set of products. Such microbes are then utilised in fermentation-based production processes. A variety of microbes have been modified for commercial production. Metabolic engineering methods and techniques are becoming more mature and diverse chemicals can be produced on a commercial scale by engineered organisms.

Advanced fermentation techniques exploiting metabolic engineering have been adopted by the chemical industry to produce alcohols and other organic compounds on a large (multi-tonne) scale. Industrial R&D efforts are ongoing to optimise genetic

[14] Report of the Sixteenth Session of the Scientific Advisory Board, (SAB-16/1, dated 6 April 2011), paragraph 14.

[15] http://www.opcw.org/about-opcw/subsidiary-bodies/scientific-advisory-board/. The reports are: First Meeting, Annex 3 of SAB-17/1, dated 23 November 2011; Second Meeting. Annex 3 of SAB-19/1, dated 12 September 2012; Third Meeting, SAB-20/WP.3, dated 11 April 2013; Fourth Meeting, SAB-21/WP.2, dated 25 November 2013.

modifications to organisms that can be used in high yield fermentation processes to produce specific chemicals. The availability of renewable carbohydrate feedstocks, such as corn grain and sugar cane, provide key economic and environmental drivers for these new commercial processes.

Processes for utilising cellulosic plant material (the cell walls of plants), which otherwise might be treated as waste, have also been developed. Cellulosic ethanol is a renewable, advanced biofuel produced by converting the starch extracted from cellulose into sugars and fermenting the sugars into ethanol. Agricultural by-products such as corn stover and cereal straws are the most commonly used renewable feedstocks today. Engineered yeasts and bacteria are being used in process development plants and large scale production facilities around the world to produce ethanol as well as other products.

Enzymes/Biocatalysts

Enzymes are large biological molecules (proteins) that catalyse the metabolic process. Enzymes and genetically modified enzymes, along with peptides and performance proteins, can help improve performance, productivity, and environmental footprints for a biological process. There is a wide variety of commercial applications in markets such as pharmaceuticals, animal health and nutrition, cosmetics and personal care, laundry and dishwashing detergents, food and beverage production, pulp and paper and textiles processing.

Catalysts, of chemical or biological origin, are used in a high percentage of chemical production processes. Biocatalysts (enzymes), usually immobilised, are being increasingly applied in the industrial production of bulk chemicals and pharmaceuticals. To overcome the limitations of naturally occurring enzymes, directed evolution has become an important tool for improving activity, selectivity, solvent tolerance and general robustness.[16] Directed evolution involves iterative cycles of mutation, selection, and amplification.

Multi-enzyme processes are technically much more complex than single enzyme processes. For chemicals produced by multi-enzyme processes, the physical spatial organisation of enzymes has been demonstrated to increase the efficacy and yield. Such approaches have also enabled the tuneable adaptation of metabolic flux. Proteinaceous and DNA-based scaffolds have been used to spatially locate enzymes important for the production of discrete and complex chemicals. These scaffolds have been developed for use in bacteria and yeast used for industrial production.

Synthetic Biology

Synthetic biology, which overlaps and complements metabolic engineering, combines the laboratory techniques of genetics and molecular biology with insights and theoretical tools derived from engineering, computer science and electronics, to design new,

[16] M. Wang, S. Tong, H. Zhao, *Bioresource Technology*, 2012, **115**,117-125.

purposely-constructed biological components and systems. This moves beyond traditional biochemical techniques, e.g. recombinant DNA technology, by incorporating engineering principles such as design control and standardised components. For example, in the same way that an electronic circuit (or other engineering design) depends upon the availability of standardised and interchangeable components and parts, a major goal of the synthetic biology community is to provide and curate a repository of well-characterised modular biological components such as proteins, gene cassettes, and plasmids.[17]

In line with this analogy, these components can be programmed to behave as biological analogues of the 'switches', 'oscillators' and 'logic-gates' used in engineering and electronic circuit construction. Such modules can then be assembled into new biological pathways or biological 'machines' that are tailored to perform specific functions. In turn, these individual units may be combined into larger more complex systems.[18,19] The use of *systems biology* approaches, aided by sophisticated computer algorithms, to analyse the behaviour of the resulting system is an integral component of such endeavours.[20]

One advantage of this modular approach is that the intensive and often repetitive lab work required in conventional laboratory genetic engineering and molecular biology techniques can often be significantly reduced. The objective of adopting these approaches is to reduce resource and time requirements in the building of sophisticated biological machines by using pre-fabricated parts.

The application of engineering approaches to biology also allows those with fewer skills and less experience to accomplish more and in less time than in the past. This is illustrated through the International Genetically Engineered Machines (IGEM) competition.[21] This predominantly undergraduate competition allows student teams to use standard interchangeable molecular parts, over the course of a summer, to produce tailored organisms. For example, the winner in 2012 developed a bacterial sensor to detect spoilage in meat. There has been rapid growth in the numbers participating in the competition. In 2013, over 250 teams with 2500 members from around 30 countries participated. There are now 17,000 alumni around the world.

Achievements in Metabolic Engineering and Synthetic Biology

The techniques and strategies of synthetic biology have already found many useful applications. Examples are the re-programming of microorganisms to produce biofuels by manipulating metabolic and biosynthetic pathways,[22, 23] and the production of drugs that are difficult to synthesise or which otherwise would need to be extracted from scarce

[17] J. C. Anderson, J. E. Dueber, M. Leguia, G. C. Wu, J. A. Goler, A. P. Arkin, et al; *Journal of Biological* Engineering, 2010, **4**, 1.
[18] P. E. Purnick, R.Weiss; *Nature Reviews Molecular Cell Biology*. 2009, **10**, 410-422.
[19] A. S. Khalil, J. J. Collins; *Nature Reviews Genetics*, 2010, **11**, 367-379.
[20] Y. N. Kaznessis, *Biotechnology Journal*, 2009 **4**, 1392-1405.
[21] http://igem.org
[22] H. Alper, G.Stephanopoulos; *Nature Reviews Microbiology*. 2009, **7**, 715-723.
[23] J. D. Keasling, *Science*, 2010, **330**, 1355-1358.

raw materials. Recent examples include the production of anthranilic acids such as the anti-allergic tranilast in modified yeast strains,[24] and the production of terpenoid compounds,[25, 26] which form the basis of perfumes and many drugs, including novel antimicrobial drugs. One of the most impressive examples has been the synthesis by engineered yeast strains of artemisinic acid, a key and very expensive intermediate for the anti-malarial drug artemisinin.[27, 28] This intermediate is difficult to synthesise and is currently prepared from scarce plant material in yields that cannot satisfy global demand for the drug. By introducing the relevant genes from the artemisia plant into yeast (*Saccharomyces cerevisiae*), synthetic biologists at the University of California were able to generate high yields of artemisinic acid.[29]

A survey of synthetic biology products published in 2012 provides additional insight into applications under development.[30] The survey identified 68 products across seven sectors (including biofuels, chemicals, energy, food, materials, and medicine) being developed by companies in 10 countries.

Chemical production was the largest sector, with 25 products including both bulk and fine chemicals. Around half of the products identified were already available, or had been demonstrated and were seeking a market, have an existing pilot plant, are in clinical trials, or are the subject of joint ventures.

Relevance of Metabolic Engineering and Synthetic Biology to Convergence Issues within the OPCW's Remit

The main issue of concern for the OPCW is whether this technology could be misused to synthesise toxins, other toxic chemicals or their precursors, in quantities that could pose a threat to the Convention. This was one area identified by the 2010 Beijing workshop discussed in Section 1.

That such a scenario is at least conceivable is shown by the example of artemisinic acid described in the section above on "Achievements in Metabolic Engineering and Synthetic Biology".

[24] A. Eudes, E. E. Baidoo, F. Yang, H. Burd, M. Z. Hadi, F. W. Collins; *Applied Microbiology and Biotechnology*, 2011, **89**, 989-1000.
[25] J. Kirby, M. Nishimoto, J. G. Park, S. T. Withers, F. Nowroozi, D. Behrendt et al; *Phytochemistry*, 2010, **71**, 1466-73.
[26] R. Muntendam, E. Melillo, A. Ryden, O. Kayser; *Applied Microbiology and Biotechnology*, 2009, **84**, 1003-1019.
[27] C. J. Paddon, P. J. Westfall, D. J. Pitera, K. Benjamin, K. Fisher, D. McPhee, et al; *Nature*, 2013, **496**, 528-32.
[28] C. Chiarabelli, P. Stano, P. L. Luisi; *Frontiers in Microbiolgy*, 2013, **4**, 285.
[29] See reference 27.
[30] Survey from Woodrow Wilson Center (Washing DC, USA), www.synbioproject.org/library/inventories/applications_inventory/.

These advances in metabolic engineering and synthetic biology make use of a wide variety of enabling technologies. They allow more to be accomplished with fewer human resources in a shorter time frame and continue to evolve rapidly.

The TWG was briefed on enabling technologies identified in background material prepared for reviews of developments in science and technology under the Biological Weapons Convention, including advances in: characterising biological systems and networks; [31] manipulating biological systems and networks; [32] engineering biological systems and networks, such as synthetic biology; gathering and manipulating biological information;[33] and converting biological information into digital data and back.[34]

The extent of use of biologically mediated synthesis in commercial chemical production (TOR 3a ii)

Commercial production of chemicals using biological processes is increasing significantly, with 10% of all chemical volume expected to be produced using these methods by the year 2020.[35] A number of commodity chemicals, organic acids (e.g. lactic acid), acetone-butanol-ethanol, and 1,3-propanediol are already manufactured on a large scale (greater than 50,000 tonnes per year) using biological processes. Commercial production of biofuels (ethanol, isobutanol) is also a reality as an additive to or substitute for petroleum based fuels. Other large scale bio-production facilities are in the planning phase or are operational; these include production plants for succinic acid, 1,4-butanediol, acrylic acid and adipic acid.

Production of more complex organic molecules is also now a reality using custom designed *biological processes* and synthetic biology platforms. As an example, there is a new large scale production facility that started up in 2012 producing farnesene, a C_{15} terpenoid chemical. Farnesene is used as a building block for more complex chemicals such as squalene, and the artemisinin intermediate artemisinic acid.

The use of biotechnology is becoming increasingly global in nature with new bio-based chemical production facilities located in Asia, North and South America and Europe. In addition to commercial considerations, the location of a bio-based facility also takes into consideration the availability of renewable feedstocks to supply the new production unit. For example, the use of waste biomass from palm oil production in Malaysia.

The following factors are driving the chemical industry to develop new biological processes to replace or supplement established chemical production methods:

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[31] Such as advances in genomics, proteomics, transcriptomics, metabolomics, fluxomics, epigenomics, and integrating data from different –omics

[32] Such as gene silencing, zinc finger nucleases, TALENs, and CRISPR

[33] Such as programming languages, data mining, dealing with large data sets, modelling and simulation, as well as online tools and software

[34] Such as gene sequencing and synthesis technologies

[35] ICIS Chemical Business, April 2-15, 2012 Edition, Article: "Biomass chemicals to be competitive in 10-15 years", page 24.

- Advances in biotechnology techniques that enable the modification of organisms and enzymes to produce specific compounds in high yields.

- Sustainability and a drive to use green chemistry; the latter can also be a cost benefit. Biological processes may use milder operating conditions, and generate fewer by-products with less waste.

- The volatility of crude oil prices: over the last 20 years, crude oil prices have increased fourfold, which has resulted in higher costs for petroleum-based products. The high price of petroleum, and at times the limited availability of some petroleum-based feedstocks, has created a commercial opportunity for cost competitive biological processes that use renewable feedstocks to produce the same chemical.

- Industrial collaboration is being leveraged where two or more companies combine their technical and commercial expertise, and intellectual property, to form partnerships to develop new biological processes and bring innovative, cost competitive products to the marketplace. Innovations are often driven by start up companies that are then acquired by larger partners. The long term trend for the use of advanced biological process routes in commercial production facilities is expected to continue. It should be noted that commercialisation of new technologies takes time and involves substantial economic risk due to the significant investment of company resources and capital. It normally takes a number of years for process development, pilot plant scale-up, start-up and then successful demonstration of a commercial facility.

The use of biologically mediated techniques for the synthesis of toxic chemicals and the application of biologically mediated processes for the synthesis/production of toxins and bioregulators, and future trends (TOR 3a iv and 3a iii)

Scheduled Chemicals

The TWG discussed the possibility and likelihood of toxic chemicals or their precursors being produced by biologically-mediated processes. It concluded that for classical chemical warfare agents, such as nerve agents and blister agents, there is no currently known advantage in trying to produce such chemicals through biological means. Regarding other toxic chemicals, it is more likely that biomediated processes would be applied to produce a precursor, particularly as the toxic chemical may have biocidal activity.

As advances in biotechnology progress, the feasibility and practicability of synthesising precursor chemicals, Schedule 1 chemicals, and other toxic chemicals by biological means may become more of a reality. It is recommended that the SAB continue to

monitor advances in the biotechnology industry on the range of chemicals being studied and produced using biological or biologically-mediated processes.

It was noted that natural metabolic pathways exist for the preparation of biological molecules containing phosphorous (P), sulfur (S), and fluorine (F), therefore making it conceivable that PSF chemicals could be obtained using biologically mediated techniques. A recent example has demonstrated the modification of polyketide synthase pathways to prepare organofluorine compounds *in vitro* and *in vivo*.[36] The TWG did not identify any industrial applications for these methods.

The TWG concluded that, at this time, the development of biomediated processes to produce scheduled chemicals as warfare agents would be more difficult than to obtain such materials by traditional synthetic chemistry.

Toxins

Toxins span a wide range of chemical types, with molecular masses less than 500 Da to large proteins of molecular mass > 100,000 Da. Saxitoxin (a small but structurally complex chemical, molecular mass 301) and ricin (a glycosylated protein, molecular mass approx. 65,000 Da) are the only toxins specifically included in Schedule 1 of the CWC.

The natural metabolic pathways have been published for the production of saxitoxin, ricin and many other toxins. *In vitro* biosynthesis of ricin and saxitoxin has been described.[37] However, the small quantities of saxitoxin required for test kits for paralytic shellfish poisons are still obtained by extraction from the natural sources, shellfish and/or cyanobacteria.[38]

Awareness and concerns about ricin have been growing as a result of incidents of misuse. Recent research has focused mainly on toxicity, detection, countermeasures, and medical applications (e.g. immunotoxins for cancer therapy).

A literature review was conducted on the application of biologically mediated processes for the production of ricin, which has been used as a model for other proteinaceous toxins. A draft genome sequence of the ricin producing castor bean has been published.[39] Although the feasibility of biologically mediated synthesis of ricin, the separate A- and B- chains, and their analogues have been demonstrated, castor beans remain the main (and potentially abundant) source of crude and pure ricin. Extraction and purification processes are technically simple and inexpensive.

[36] M. C. Walker, B. W. Thuronyi, L. K. Charkoudian, B. Lowry, C. Khosla, M. C. Y. Chang, *Science*, **341**, 2013, 1089-1094.
[37] K. D. Cusick, G. S. Sayler, *Mar. Drugs*, **11**, 2013, 991-1018; and references therein.
[38] See for example WO/2010/109386 A1, 'Method for the Industrial Purification of Biologically Active Phytoxins'.
[39] A.P. Chan et al; *Nature Biotechnol*., 2010, **28,** 951-956

The TWG concluded that, at present, obtaining ricin, and the small quantities of saxitoxin required for permitted purposes under the CWC, from their natural sources is simpler than employing metabolic engineering strategies. It was however noted that as enabling technologies become less expensive, more efficient, and more available, this assessment may need revising.

Bioregulators

Bioregulators are endogenous chemicals that mediate a wide range of body processes, including control of blood pressure, airway compliance, and functioning of the gastro-intestinal system. In the brain they modulate sleep, mood, cognisance and behaviour. Bioregulators encompass a wide range of chemical classes, including peptides, small proteins (polypeptides with approximately 50 amino acid residues or more), nucleotides, lipid derived metabolites, and small molecules such as neurotransmitters.

Peptides composed of short chains of amino-acids (typically from 2-50 residues), comprise the largest group of bioregulators, and have been the class for which commentators on the CWC have expressed most concern for misuse, mostly in the context of new incapacitants.[40] However, peptides have inherent disadvantages as potential CW agents or incapacitants. As part of the body's control mechanism, they are rapidly degraded by endogenous enzymes in the body, most are poorly absorbed through biological membranes such as the lung and the blood brain barrier, and they would be expensive to manufacture (though costs for pharmaceutical use of peptides have fallen in recent years). No data has been published that suggests that any individual centrally acting peptide should be regarded as a chemical of concern, and the stability of peptides towards weaponisation and dissemination is apparently unknown. Some peptides that cause bronchoconstriction, e.g. substance P, have been reported to have moderate to high inhalation toxicity in small rodent species. Such peptides interact with receptors on the surface of the lung which does not require penetration of membranes.

The shortcomings of peptides as drugs (and by implication for uses prohibited by the Convention) can be moderated in several ways. Formulations, particularly associated with liposomes or nanocarriers, are being explored to enhance penetration of the blood brain barrier, overcome host defences, and target specific organs. Drug companies have screened large numbers of metabolically resistant analogues, mostly with unnatural (chemical) modifications, some of which may have substantially increased potency and toxicity. However, such modifications may add to the complexity and cost of the end product. The potential of peptides for development as incapacitants may therefore have been overstated by some commentators.

Substantial advances in production methods for peptides have been made in the last two decades. Although they could be produced in genetically modified organisms, the pharmaceutical industry currently regards chemical synthesis as the most cost-effective method for producing many small peptides.

[40] J. B Tucker, *Bulletin of the Atomic Scientists*, 2010, **66**, 56-66.

Although the concern for bioregulatory peptides may have been somewhat overstated, it is recommended that the TS increase and maintain in-house knowledge of bioregulators and possible delivery systems.

Other types of bioregulators should also be noted. For example, some of those derived from lipid pathways, such as eicosanoids (prostaglandins, thromboxanes, leukotrienes) and platelet activating factor, have high physiological activity, and in some cases high toxicity (particularly metabolically less labile analogues). These have mostly been synthesised through multistage chemical processes, although biologically mediated stages are known.

Chemical synthesis of agents of biological origin (e.g. bioregulators) and of replicating systems (TOR 3b)

Toxins and Bioregulators

The chemical synthesis of most toxins remains a serious challenge to organic chemists. Although many low molecular mass toxins such as saxitoxin have been synthesised through the combined efforts of highly skilled teams, the TWG was not aware of any examples that could be considered a serious threat to the purposes of the CWC. The purely chemical synthesis of proteins such as ricin is feasible but impractical.

Substantial advances in production methods for peptides have been made in the last two decades, and, as referred to in paragraph 2.35, the pharmaceutical industry currently regards chemical synthesis as the most cost-effective method for producing many small peptides, using combinations of solid phase and solution synthesis. This probably applies particularly to peptides with unnatural modifications. Peptide production requires specialised equipment. Extension to the chemical synthesis of full length proteins, despite advances in synthetic chemical strategies, is currently limited in its scalability.[41] Most other types of bioregulators have been synthesised without the intervention of biologically mediated processes.

The group concluded that although the technical capability to chemically synthesise many toxins, bioregulators, and other physiologically active peptides exists today, there are practical limitations with regard to scale and complexity. The threat of possible misuse of this technology with regard to the CWC is therefore currently considered low.

Nucleic Acids

Nucleic acid coupling technology has increased substantially in its efficiency and it is now possible to purchase full length genes and synthetic genomes from commercial sources. This has been a major enabling factor in synthetic biology, together with parallel advances in nucleotide sequencing. Production of synthetic genomes is not error free and there are still challenges to be overcome with these technologies.[42] However,

[41] J. M. Chalker, *Chem. Biol. Drug Des*, **81**, 2013, 122-135.
[42] S. Ma, I. Saaem, J. Tian, *Trends in Biotechnology*, **30**, 2012, 147-154.

given the available methodologies for genetic engineering and manipulation of genes *in vivo*, limitations of full length gene synthesis are not an insurmountable obstacle for using metabolic pathways to produce useful or toxic substances.

Viruses and Bacteria

A broad range of viruses can now be chemically synthesised. The first, and perhaps best known example, was the synthesis of the polio virus in 2002.[43] This was followed, for example, by the synthesis of: φX174 bacteriophage;[44] the strain of influenza virus responsible for the 1918 pandemic;[45] and the coronavirus responsible for SARs.[46] The group noted that the technologies that enable the chemical synthesis of viruses are becoming more accessible but the intangible skills required remain in relatively few facilities.

A key achievement of synthetic biology would be the creation of a living organism *ab initio*.[47] Significant progress was made towards this end when a team from the J. Craig Venter Institute inserted a synthetic 'minimal genome' cloned in yeast into a recipient bacterial *Mycoplasma capricolum* cell,[48] from which the natural genetic material had been removed. The resulting organism was functional in that it could survive, grow, and reproduce itself. Since the cytoplasm and cell membrane of the recipient cell were intact, these workers cannot be said to have created a synthetic organism from scratch (i.e. using only raw chemical precursors), but such an achievement is probably only now a matter of time and technique.

Whether any biotechnological processes exist, other than biologically mediated synthesis, that are of relevance to the implementation of the CWC; (i.e. whether the types of production equipment and processes may pose a significant risk to the object and purpose of the Convention) (TOR 3c)

The findings of the TWG in regard to biological processes, production equipment etc and other applications of biotechnology relevant to the CWC are covered under the other TORs.

The Meaning of "Produced by Synthesis" as per subparagraph 1(a) of part IX of the CWC Verification Annex (TOR 3d)

A key issue in the implementation of Part IX of the Verification Annex (VA) for Other Chemical Production Facilities (OCPF) is whether biological or biologically-mediated processes are covered by the term "produced by synthesis". This term is used as a basis

[43] J. Cello, A. V. Paul, E. Wimmer; *Science,* 2002, **297**, 1016-1018.
[44] H. O. Smith, C. A. Hutchison, C. Pfannkoch, J. C. Venter; *PNAS*, 2003, **100**, 15440-15445.
[45] T. M. Tumpey, et al; *Science,* 2005, **310**, 77-80.
[46] M. M. Becker, et al; *PNAS*, 2008, **105**, 19944-19949.
[47] See reference 28.
[48] D. G. Gibson, J. I. Glass, C. Lartigue, V. N. Noskov, R. Y. Chuang, M. A. Algire, et al ; *Science*. 2010, **329**, 52-56.

for declarations under the CWC of Discrete Organic Chemicals (DOCs), as it is applied to Part IX of the Verification Annex. However, the meaning of term "produced by synthesis" remains open to interpretation by States Parties and this has resulted in different practices adopted by States Parties when declaring OCPFs employing biologically-mediated processes.

The TWG reviewed this matter in depth, including the historical development and use of the term. Taking into consideration the convergence of chemistry and biology as it relates to the synthesis of chemicals, the TWG was of the view that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis"**.** The SAB has subsequently endorsed this recommendation (SAB-19/1, dated 12 September 2012 and RC-3/DG.1, dated 29 October 2012).

As already noted, there has been a significant increase in the commercial development and production of chemicals using biological and biologically mediated processes over the past 5-10 years and this trend is expected to continue. The TWG noted that a significant percentage of these facilities will be producing organic chemicals in quantities more than 200 tonnes/year, and this should make them declarable under Part IX of the Verification Annex. The degree of relevance to the object and purpose of the Convention for these new bio-based facilities will need to be further assessed by the TS, SAB, and policy making organs. This assessment would also serve as a basis on whether there are grounds to consider an exemption from declaration or a need to review thresholds for declaration and inspection of OCPFs. This issue will be taken up by the TWG on Verification at its Third Meeting (See SAB-21/WP.1, dated 25 September 2013).

The TWG advises the TS to undertake a review of the technical feasibility of converting a bio-based chemical processing facility to produce chemicals of concern to the CWC (such a review could fall under remit of verification TWG).

The potential benefits to the CWC of the convergence of chemistry and biology (which might include e.g. protective measures, medical countermeasures, and diagnostics) (TOR 3e)

Medical Countermeasures

Advances associated with the convergence of chemistry and biology offer many potential benefits in chemical defensive countermeasures, in terms of therapeutics, diagnosis of exposure, decontamination, physical protection and detection. Significant advances are being made in development of protein and antibody-based drugs as effective medical countermeasures against chemical warfare agents,[49,50] although none has yet been approved for human use. Recombinant human butyrylcholinesterase (BuChE), derived from the milk of transgenic goats or CHO cell expression systems, is a candidate for prophylactic or post-exposure treatment of nerve agent poisoning by stoichiometric (1:1)

[49] P. Masson, *Toxicol. Lett.*, 2011, **206**, 5-13.
[50] R. B. Reisler, L. A. Smith; *Adv. Prev. Med.*, 2012, **2012**, 149737-149740.

scavenging of the agent.[51] A disadvantage of BuChE is that a large amount of proteinaceous enzyme must be administered; engineered hydrolytic enzymes are being sought as alternatives (see also the next section of this report on Enzymes for Decontamination), each molecule of which could hydrolyse many molecules of nerve agent. Monoclonal antibodies based on synthetic haptens could also effectively bind or hydrolyse the nerve agent.[52] Gene therapy could be a method for introducing catalytic or stoichiometric bioscavengers *in vivo*. A gene-delivered human paraoxonase 1 (hPON-1, a hydrolytic enzyme) using adenoviral vector has demonstrated endogenous production of high levels of hPON-1, which provides effective protection against nerve agents.[53] Other approaches include gene therapy involving introduction of human BuChE or acetylcholinesterase (AChE) genes into cells for therapeutic purposes. Enhanced drug delivery systems, e.g. based on nanotechnology, may provide more effective protection or treatment than current drug formulations.

The OPCW SAB has previously reported on current practices for medical treatments and countermeasures in their report on science and technology to the Third Review Conference (see RC-3/DG.1). The SAB was asked at its Twentieth Session to update this information in greater detail (see SAB-20/1, dated 14 June 2013). A SAB report to the TS is in preparation, recommending pre-treatments, vaccines, emergency care, and long-term treatments that are currently available for blister and nerve agents; plus the most relevant information sources that can be monitored to keep abreast of new developments in medical countermeasures.

Enzymes for Decontamination

Enzymatic approaches to the decontamination of chemical warfare agents are being developed. These are generally less aggressive than currently used decontaminants, with logistical and environmental advantages over chemical and physical approaches.

Naturally occurring bacterial enzymes (phosphotriesterase, PTE, and organophosphorus acid anhydrolase) have been isolated that catalyse the hydrolysis of organophosphate nerve agents with high rate enhancements and broad substrate specificity. Mutant forms of these enzymes have been constructed through rational redesign of the active site binding pockets and random mutagenesis to create protein variants that are optimised for the detoxification of agricultural insecticides and chemical warfare agents.[54] In contrast to the wild-type enzymes, PTE mutants have been engineered, which demonstrate a strong preference for the Sp enantiomers (the more toxic form) of sarin, soman, cyclosarin, VX and VR agents. One enzyme with 11 mutations proved 15,000 times more effective than wild type PTE in breaking down cyclosarin.

Prototype enzyme formulations have been developed that are highly selective for G-type nerve agents such as sarin, soman, and related organophosphate chemicals, or

[51] F. Nachon, X. Brazzolotto, M. Trovaslet, P. Masson; *Chem. Biol. Interact*., 2013, **206**, 536-544.
[52] P. Jia, Y. Wang, M. Yu, J. Wu, R. Yang, Y. Zhao, L. Zhou; *Toxicol. Lett.*, 2009, **187**, 45-51.
[53] See reference 52.
[54] F. M. Raushel, *Current Opinion in Microbiology*, 2002, **5**, 288-295.

which are highly selective for VX, Russian-VX, and pesticides such as parathion. These are not yet commercially available. Both products contain an industrial-grade enzyme and a buffering mixture in one small, convenient package. They have low toxicity, are non-corrosive, easy to use, and water-soluble.

Protective Equipment

Developments in the convergence of chemistry and biology, and nanotechnology, have influenced new research approaches to physical protective equipment. Current research is directed primarily at systems which enhance protection but with reduced physiological burden for the wearer, and which are less cumbersome. There are also research efforts to develop self decontaminating protective clothing, e.g. with the incorporation of enzymes and/or catalysts.[55, 56, 57] The TWG noted that it is difficult to improve on carbon as a filter material for canisters, as well as for protective clothing, due to its adsorbent properties and relatively low cost. Layers of carbon cloth and carbon fibres are a promising approach to maintaining adsorption properties whilst reducing the physiological burden of respirator filters. Research efforts are also underway to develop nanomaterials as effective gas mask canister adsorbents and for protective clothing,[58, 59] which may have a lower burden for the wearer than current systems. The benefits of these research efforts are just starting to unfold. It can be a difficult and time consuming process to take a promising equipment breakthrough from an ideal lab environment to a field tested, commercially available item.

Detection and Biosensors

Although the majority of fielded CW agent detectors and monitors rely on physicochemical principles, detectors with biological sensing elements have been in service for more than 40 years. Most of these use inhibition of the enzymes AChE or BuChE for the detection of nerve agents. AChE is the biochemical target mediating the toxicity of nerve agents, and BuChE is a related enzyme which acts as a partial scavenger (see discussion on bacterial enzymes in the "Enzymes for Decontamination" section above). These enzymes have been employed in automated vapour detectors, wet chemistry kits, tickets and Draeger-type tubes, and provide sensitive devices for the generic detection of nerve agents. Advances in enzyme immobilisation techniques played an important part in the development of these detectors. More recently, a disclosure spray[60] based on BuChE has been commercialised.

Most of the recent developments employing biological sensing elements for nerve agents have been in prototype miniaturised disposable biosensors, either for the direct detection

[55] A. J. Russell, et al; *Annual Review of Biomedical Engineering*, 2003, **5**, 1-27.
[56] Schreuder-Gibson, et al; *MRS Bulletin*, 2003, **28**, 574-578.
[57] Q. T. Truong, B.E. Koene; *Current Nanotech*, 2013, **1**, 663-666.
[58] G. Hong-ze, et al; *Journal of Chinese People's Armed Police Force Academy*, 2011, **12**.
[59] M. Jahangiri, et al; *Iranian Journal of Environmental Health Science & Engineering*, 2013, **10**, http://www.ijehse.com/content/10/1/15.
[60] Agentase Disclosure Spray. Technical Information Summary. U.S. EPA ORD NHSRC April 2009. www.epa.gov/nhsrc/pubs/TISAGentaseDisclosureSpray.pdf. Accessed 03/11/13.

of OP nerve agents, or pesticides with similar AChE inhibitory activity, or as point-of-care (POC) diagnostic devices for detecting inhibited cholinesterase in cases of exposure.

A biosensor incorporates a biological sensing element (e.g. enzyme, antibody, cell, receptor, organism), closely integrated with a transducer which converts the response to an electrochemical, optical or other signal, plus amplifying and display components. Recent trends have been towards miniaturised disposable devices, many constructed with nanosized materials for transduction, and as a support for the sensing element. The current world market for such devices is estimated to be around USD 13 billion, a major application being glucose monitors for diabetics. More than twenty experimental/prototype devices have been described for OP nerve agent or pesticide detection, or for diagnosing exposure to such compounds. Biorecognition elements include AChE and BuChE, and OP hydrolysing enzymes such as PTE. The use of immunoassays has been limited by a lack of suitable antibodies, either to the agents or to phosphylated cholinesterase. Future developments are likely to include improved enzymes, antibodies and immobilisation techniques, and further exploitation of nanotechnology. A biosensor for sulfur mustard (based on antibodies) is commercially available.

Biological sensing in the form of various types of immunoassay, other types of biorecognition, or other types of bioassay, has long been a major component of detection systems for saxitoxin and ricin. Research to develop portable or disposable biosensors is in progress.

An additional avenue for current research is the development of broad spectrum or specific detection systems designed to utilise sensor proteins used in olfactory processes (to mimic the high sensitivity of sniffer dogs).

Primary diagnostic tools could be useful for a variety of on-site inspection related activities The TWG suggests that the OPCW TS consider such technologies as they become commercially available (this could fall under the remit of the TWG on Verification).

Whether there are other scientific disciplines, apart from biology, that are converging in a significant way with chemistry, and whether it is possible to identify triggers or early-warning indicators for potential game-changing events that might have implications (whether positive or negative) for the CWC (TOR 3f)

Nanotechnology

The term nanotechnology applies to functional components and materials that are smaller in size than 100 nanometers (1 nanometer = 1 millionth of a millimeter) in at least one dimension, and which have physical, chemical or biological properties that differ significantly from those at a larger scale. Nano-sized particles have a high surface area to mass ratio which may impart higher chemical reactivity, increased strength, and altered electrical properties. They may also exhibit altered optical and magnetic properties.

As reflected in the 2012 SAB Report on S&T to the Director-General (RC-3/DG.1), nanotechnology is a rapidly expanding technology, converging with other sciences such as chemistry, biology and physics, that may have significant implications for the Convention. The European Commission has estimated the global market for nanomaterials at EUR 20 billion and forecast products underpinned by nanotechnology to grow from a global volume of EUR 200 billion (2009) to EUR 2000 billion in 2015.[61] Nanotechnology is contributing to major advances in materials science, medicine, electronics and energetics.

Nanocarriers for drug delivery: in medicine, nanoparticle-based formulations are being widely explored for enhanced or 'smart' drug delivery. Examples are controlled drug release, enhanced penetration of the blood brain barrier (e.g. for therapeutic peptides), and targeting specific organs or cells (e.g. cancer cells). Nano-particles most commonly used in drug formulations include: imprinted polymers, dendrimers, vesicles, nano-spheres, nano-capsules, micelles, carbon nano-tubes, liposomes, and nano-emulsions. Additional bio-based nanocarriers are being researched including DNA-based systems[62] and viral-based systems.[63] These drug nanocarriers can be comprised of a variety of materials (e.g. organic, mineral, and composite) and architectures (e.g. spheres, rods, and tubes). Allied to these advances in therapeutics, nanotechnology is contributing to major developments in diagnostics.

Nanocarrier-based delivery systems present several advantages over the classic ones: overcoming solubility problems, protecting the drug from the external environment (temperature, UV radiations, pH), and controlling the release profile. Nanocarrier-based delivery systems permit a more precise and controlled targeting at the site of action, while reducing the time of exposure at non-targeted tissues. This can increase efficacy, and reduce toxicity and side effects. Improved efficacy of cancer treatment illustrates the use of nanocarriers (e.g. tumour targeted delivery of Taxol is in clinical trials) [64].

Nanoparticles are also finding applications in sensor and detection technologies, protective materials, and decontamination (as described in the previous section on advances in protection). Other aspects of nanotechnology, including the possible toxic hazard associated with some nanoparticles and beneficial applications to chemical defense, were considered by the SAB in their 2012 S&T report (see paragraphs 53 and 54 of RC-3/DG.1).

As with advances in synthetic biology, nanotechnology has some potential for application to purposes prohibited by the CWC. The enhanced delivery of therapeutic drugs to their biochemical target could be exploited for the delivery of toxic chemicals, although there is a considerable difference between a chemical weapon and a high value pharmaceutical.

[61] http://ec.europa.eu/nanotechnology/index_en.html
[62] J. Li, C. Fan, H. Pei, J. Shi, Q. Huang; *Adv Materials*, 2013, **32**, 4386-4396.
[63] Y. Ma, R. J. M. Nolte, J. J. L M. Cornelissen; *Advanced Drug Delivery Reviews*, 2012, **64**, 811–825.
[64] See for example, S. Strieth, et al.; *Head & Neck*, 2013, DOI: 10.1002/hed.23397.

Other Scientific Disciplines

The TWG noted that a broad range of scientific disciplines are converging; including: chemistry; biology; materials science; computer science; engineering; information theory; network theory, mathematics; and quantum mechanics. Scientific practices, across all fields, continue to evolve using multi-disciplinary approaches.

The temporary working group will also advise on how to bring together expertise on the Biological Weapons Convention and Chemical Weapons Convention in order to discuss areas of common interest between the two Conventions and share knowledge related to convergence (TOR 4)

Many of the issues raised in this report impact both the BWC and the CWC. The TWG provided a unique vehicle for interaction of experts from the two disarmament treaties. This has been beneficial to both the OPCW SAB, and the BWC Implementation Support Unit, and should continue.

Using convergence as a focus point has provided opportunities to share experiences of CWC and BWC experts on the effective monitoring of scientific developments, understanding the impact of advances in S&T, and to jointly participate in education and outreach activities on the importance of S&T in disarmament. The TWG recommends that the SAB and TS continue to work across all of these areas.

Side events held in the margins of BWC meetings and scientific conferences provided forums for the OPCW Technical Secretariat and the SAB to interact with experts from the BWC outside of the TWG meetings.[65] The TS, supported by the SAB, should continue to participate in such meetings and continue to address convergence.

3. Conclusions and Recommendations

On developments in biological and biologically-mediated processes:

Bulk and fine chemicals are being produced increasingly using biologically mediated processes.

- ***Recommendation 1***: **The SAB, or a suitable TWG, and the TS should continue to monitor advances in production facilities and technologies, and related trends such as outsourcing and modularisation of equipment. Assessments should be made on a periodic basis to determine their relevance to verification under the CWC. Regular engagement with subject matter experts, e.g. from the biotechnology industry, will be required.**

[65] Side events were held at the BWC Meeting of Experts in 2012 and 2013, the BWC Conference of States Parties in 2012 and 2013, and on the margins of a conference on Synthetic Biology (SB6.0) held in July 2013. Future events are being planned.

Metabolic engineering approaches have improved the activity, selectivity, solvent tolerance and general robustness of biocatalysts or enzymes for an increasing range of chemical reactions. Synthetic biology is reducing the barriers to entry, necessary resources and time requirements for building customised biological machines. Both approaches make use of a wide variety of enabling technologies. It is at least conceivable to use these approaches to synthesise toxic chemicals, toxins, bioregulators, or their precursors, in quantities that could pose a threat to the convention. These technologies are also producing benefits to the CWC, including in medical countermeasures (covered by a separate report of the SAB), decontamination, protective equipment, detection and biosensors.

- ***Recommendation 2:*** **The SAB should monitor developments in biological and biologically-mediated chemical production processes, such as metabolic engineering, synthetic biology and associated enabling technologies**. **Regular engagement with subject matter experts will be required.**

On scheduled chemicals:

Although metabolic pathways are known for some PSF chemicals, there are no known advantages in trying to produce classical chemical warfare agents, such as nerve agents or blister agents, through biological means.

- ***Recommendation 3*****: The SAB should continue to monitor the range of chemicals being studied and produced using biological or biologically-mediated processes.**

- ***Recommendation 4*****: The SAB, or a suitable TWG, should review advances in rational enzyme design prior to the next review conference**.

On toxins:

Although the technical capability to chemically synthesise many toxins exists today, there are practical limitations with regard to scale and complexity. The threat of possible misuse of this technology with regard to the CWC is therefore currently considered low. Synthetic biology approaches could be used to produce toxins. In vitro production of the scheduled toxins saxitoxin and ricin has been demonstrated. However, obtaining proteinaceous toxins such as ricin in quantity from their natural sources is simpler than through employing metabolic engineering or synthetic biology approaches. Obtaining saxitoxin from its natural sources, though inefficient, is sufficient to supply the small quantities required for legitimate needs but would not be appropriate for CBW scale production. Future developments in the cost, efficacy and availability of relevant enabling technologies may necessitate reviewing the likelihood of using these approaches to acquire toxins.

- ***Recommendation 5*****: The SAB, or a suitable TWG, should review the feasibility of using metabolic engineering or synthetic biology to obtain toxins prior to the next review conference**.

On bioregulators:

No data has been published that suggests that any individual centrally acting peptide should be regarded as a chemical of concern. Naturally occurring peptides are usually rapidly metabolised and are poorly absorbed through biological membranes such as the lung and the blood brain barrier. They can be chemically modified to illicit increases in potency and toxicity but resulting in extra complexity and cost. Advances in nanotechnology are being used to enhance penetration of the blood brain barrier, overcome host defenses, and target specific organs by therapeutic peptides and other drugs. Some peptides that cause bronchoconstriction by direct interaction with receptors on the surface of the lung have been reported to have moderate to high inhalation toxicity in small rodent species. Other types of bioregulators have high physiological activity, and in some cases high toxicity.

The potential of peptides for development as incapacitants may have been overstated by some commentators. Peptides could be produced using metabolic engineering and synthetic biology but the pharmaceutical industry currently regards chemical synthesis, using specialized equipment, as the most cost-effective method for producing many small peptides. The threat of possible misuse of this technology with regard to the CWC is currently considered low.

- ***Recommendation 6*: The TS should increase and maintain in-house knowledge of bioregulators, and possible applications of new developments in drug delivery.**

On replicating organisms, such as bacteria and viruses:

A broad range of viruses can now be chemically synthesised. Work is ongoing towards the chemical synthesis of a bacterium. The technologies that may enable the chemical synthesis of replicating organisms are becoming more accessible, but the intangible skills required remain in relatively few facilities. In most cases, and at the current time, obtaining bacteria and viruses from their natural sources, or from commercial suppliers, is simpler than through employing chemical synthesis, metabolic engineering or synthetic biology approaches.

- ***Recommendation 7*: The SAB, or a suitable TWG, should review the synthesis of replicating organisms prior to the next review conference.**

On benefits to decontamination:

Enzyme-based systems for decontaminating toxic substances are currently under development, including for nerve agents, organophosphate pesticides, and vesicants. They offer low corrosiveness, and logistical and environmental advantages over existing systems. Bacterial enzymes have been identified that break down certain nerve agents, and modified using biochemical/recombinant approaches to increase their selectivity and efficacy.

- ***Recommendation 8*: The SAB, or a suitable TWG, should review progress in the use of enzymes for decontamination prior to the next review conference**.

On benefits to protective equipment:

Developments in the Convergence of Chemistry and Biology, and particularly nanotechnology, have lead to new research approaches to physical protective equipment. Current research is directed primarily at enhancing protection whilst reducing the physiological burden and physical restrictions of respirators and clothing. Examples are the incorporation of enzymes or catalysts to develop self decontaminating protective clothing, and the use of nanomaterials with improved properties in canister filters and clothing. The benefits of these research efforts are just starting to unfold.

- ***Recommendation 9*: The OPCW should monitor advances in protective equipment and possible applications for OPCW personnel as they become commercially available**

On benefits to detection and biosensors:

Recent developments in detectors and monitors that include a biological sensing element, e.g. enzyme or antibody, have included miniaturised disposable biosensors, particularly as point-of-care diagnostic devices. Such developments have drawn significantly on advances in nanotechnology. Technologies described in this report are being applied to improve the enzymes and antibodies used as sensing elements. An innovative approach being explored for detection is the use of sensor proteins from olfactory processes. Primary diagnostic tools could be useful for a variety of on-site inspection-related activities.

- ***Recommendation 10*: The OPCW should consider possible applications of diagnostic devices to on-site activities as they become commercially available**.

On convergence with other scientific disciplines:

Nanotechnology is playing an important role in improving drug delivery to the body, protective equipment, and in the development of biosensors. Nanotechnology may have some potential for application to purposes prohibited by the CWC.

- ***Recommendation 11*: The SAB should monitor advances in nanotechnology prior to the next review conference**. **Regular engagement with subject matter experts will be required.**

A broad range of scientific disciplines are converging, including: chemistry: biology; materials science; computer science; engineering; information theory; network theory; mathematics; and quantum mechanics. Scientific practices, across all fields, continue to evolve using multi-disciplinary approaches.

- ***Recommendation 12*: The SAB and TS should examine ways to increase and maintain in-house, high level knowledge of a broader range of scientific disciplines.**

<u>On bringing together expertise on the BWC and CWC in order to discuss areas of common interest and share relevant knowledge:</u>

The TWG provided a unique international vehicle for interaction of experts from the two disarmament treaties.

- ***Recommendation 13*: A venue like the TWG on convergence of chemistry and biology should continue to exist, possibly as a temporary working group or a standing arrangement under the SAB.**

Similar interactions could be valuable at the national level and the national authorities could play an important role in building the necessary bridges.

- ***Recommendation 14*: National Authorities could be encouraged to engage more actively on convergence issues, including interacting with relevant biological and chemical scientific communities and hosting relevant events. A standing item on science and technology at National Authority Days might provide an opportunity to promote and report back on such an activity. Adopting convergence as a major theme for a future National Authority Day would help draw attention to this issue.**

There is continued value in bringing together expertise related to both treaties to consider developments in science and technology and their implications, education and outreach.

- ***Recommendation 15*: The SAB and TS should continue to work across areas of overlap between the CWC and the BWC. The Director-General might ask States to consider knowledge of the biological sciences when considering nominating experts to the SAB.**

Side events held on the margins of BWC meetings and scientific conferences provided fora for the TS and the SAB to interact with experts from the BWC outside of the TWG meetings.

- ***Recommendation 16*: The TS, supported by the SAB, should continue to participate in such meetings and continue to address convergence**.

- ***Recommendation 17*: The Director-General might consider meeting with the Chair of the BWC and heads of relevant international scientific bodies to explore issues around convergence.**

The TWG identified a number of other options for discussing areas of common interest and sharing knowledge between CWC and BWC communities, including:

- Feeding the findings of this report back to the relevant scientific communities;

- Holding a conference involving both expert communities;

- Exploring opportunities for a special edition(s) of relevant scientific journals or 'crowd-sourced' engagement through written and visual media;

- Establishing a communications technology platform or online collaborative work space to allow interested experts to continue to work on these issues; and

- Increasing coordination and collaboration between the TS and the BWC ISU on their engagement with relevant scientific communities.

<u>On the meaning of "Produced by Synthesis" as per subparagraph 1(a) of Part IX of the CWC Verification Annex:</u>

- ***Recommendation 18*: Taking into consideration the convergence of chemistry and biology as it relates to the synthesis of chemicals, the TWG was of the view that any process designed for the formation of a chemical substance should be covered by the term "produced by synthesis".**

The SAB has subsequently endorsed this recommendation. The TWG on Verification (formed in 2013) has been asked to consider the implications.

There has been a significant increase in the commercial development and production of chemicals using biological and biologically-mediated processes. This trend is expected to continue and a significant percentage of these facilities will be producing organic chemicals in quantities that should make them declarable. The degree of relevance of these facilities to the object and purpose of the CWC will need to be assessed by the TS, SAB and policy making organs. This assessment would also serve as a basis to consider whether there are grounds to exempt certain types of facilities or a need to review thresholds for declaration and inspection of OCPFs.

- ***Recommendation 19*: The TS should review the technical feasibility of converting a bio-based chemical processing facility to produce chemicals of concern to the CWC**.

4. Glossary

Acetylcholinesterase (AChE)
An enzyme that hydrolyses and terminates the action of the neurotransmitter acetylcholine.

Biocatalyst
A substance, especially an enzyme that initiates or modifies the rate of a chemical reaction in a living body; a biochemical catalyst.

Biosensor
A biosensor is an analytical device which converts a biological response into a measurable signal. It generally utilises biological components, e.g. enzymes or antibodies as the signal generating response. Such devices can be used in environmental monitoring, trace gas detection and in water treatment facilities.

Bronchoconstriction
The narrowing of air passages of the lungs from smooth muscle contraction, as in asthma.

Butyrylcholinesterase (BuChE)
An enzyme that scavenges choline esters and nerve agents; its physiological role is unknown.

Bioregulator
Chemical substances that regulate a wide range of body functions, including blood pressure, airway compliance, sleep, mood, cognisance, and behaviour. They include a wide range of chemical classes, e.g. short chain peptides, polypeptides, nucleotides, lipid-derived metabolites, and small molecules such as neurotransmitters.

Bioregulatory chemicals
Chemicals whose physiological function is to regulate cellular processes.

Bioscavengers
Molecules that act to neutralise or remove unwanted chemical species within a cell e.g. an enzyme that neutralises a reactive chemical.

Blood brain barrier
A layer of tightly packed cells that make up the walls of brain capillaries and prevent substances in the blood from diffusing into the brain: passage across the cell membranes is determined by solubility in the lipid bilayer or recognition by a transport module.

Carbon nano-tubes
A nanoscale (< 100 nm in at least one dimension) tube-like structure made up of carbon atoms.

Cellulosic
Of, pertaining to, or containing cellulose. Cellulose is a fibrous carbohydrate that acts as a structural framework of plants; indigestible by humans, but serves as a food source for many other organisms. About one-third of all plant matter is cellulose.

CHO cell expression
The use of Chinese hamster ovary cells, a common cell line in laboratories, as a system to express biological molecules.

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)
A form of DNA has been identified as a rudimentary 'immune' system against viral infections and horizontal gene transfer.

CRISPR Associated (Cas) system
A mechanism used by bacteria to incorporate into their genome, elements taken from viruses they have encountered. The system has become an enabling technology for genome engineering.

Cytoplasm
Main mass of protoplasm or cell substance.

Dendrimers
Large synthetically produced polymers in which the atoms are arranged in many branches and subbranches radiating out from a central core.

Directed evolution
Directed evolution is a method used in protein engineering that mimics the process of natural selection to evolve proteins or nucleic acids toward a user-defined goal. Directed evolution, involves harnessing natural selection at the molecular level and directing the evolution of proteins that are customised to tailor their structure and function for a desired purpose.

Disclosure spray
An enzyme based chemical agent detection system in a spray formulation.

DNA
Deoxyribonucleic acid, a self-replicating material which is present in nearly all living organisms as the main constituent of chromosomes. It is the carrier of genetic information.

Draeger-type tubes
Draeger-Tubes are glass vials, filled with a chemical reagent that reacts to a specific chemical or family of chemicals. If the targeted chemical(s) is present, the regent in the tube changes colour and the length of the colour change typically indicates the measured concentration.

Enzyme
Enzymes are proteins that act as biological catalysts.

Enzyme engineering
The branch of biomolecular engineering concerned with processes designed to produce, isolate, purify, and immobilise enzymes and tailor their function and properties.

Epigenome
The epigenome comprises all of the chemical compounds that have been added to the entirety of one's DNA (genome) as a way to regulate the activity (expression) of all the genes within the genome.

Epigenomics
Epigenomics pertains to analysis of epigenetic changes across many genes in a cell or entire organism.

Feedstocks
Materials or partially processed chemicals used to produce more complex chemicals in industrial processes.

Fluxomics
The study of the flow of fluid and molecules within cells.

Gene cassettes
A modular DNA sequence encoding one or more genes. Used in genetic engineering to incorporate genes into a longer DNA sequence.

Gene silencing
Mechanism by which cells shut down large sections of chromosomal DNA. Gene silencing can be done by incorporating the DNA to be silenced into a form of DNA called heterochromatin that is already silent. The process of gene silencing is important for the differentiation of different cell types.

Gene therapy
Gene therapy is a rapidly growing field of medicine in which genes are introduced into the body to treat diseases. Genes control heredity and provide the basic biological code for determining a cell's specific functions. Gene therapy seeks to provide genes that correct or supplant the disease-controlling functions of cells that are not, in essence, doing their job.

Gene interaction
A gene interaction is an interplay between multiple genes that has an impact on the expression of an organism's phenotype.

Genetics
The science of heredity, dealing with resemblances and differences of related organisms resulting from the interaction of their genes and the environment.

Genome
A full set of chromosomes; all the inheritable traits of an organism.

Genomics
The study of genomes.

Green chemistry
The invention, design and application of chemical products and processes to reduce or eliminate the use and generation of hazardous substances.

Hydrolysis
The chemical breakdown of a compound using a water-based chemical reaction medium (reaction with water).

Immunoassay
A procedure for detecting or measuring specific chemicals (usually proteins) through their properties as antigens or antibodies.

Immunotoxin
A monoclonal antibody linked to a toxin with the intention of destroying a specific target cell while leaving adjacent cells intact.

Imprinted polymers
Synthetic polymers with specific binding sites for a target molecule that are formed by molecular imprinting (a process that allows for the synthesis of artificial receptors for a given target molecule based on target size and shape and the properties of the polymer).

In vitro
From the Latin, meaning "within the glass". In biology, this refers to processes or reactions taking place in a test tube, culture dish, or elsewhere outside a living organism.

In vitro biosynthesis
The synthesis (production) of chemical species using biological processes in vitro.

In vivo
from the Latin, meaning "within the living", of processes or experiments taking place within the cell of a living organism.

Lipid
Molecules that consist of a hydrocarbon chain and a polar head group that make up the building blocks of cell membranes. Other biological functions of lipids include energy storage and cell signalling.

Liposome
A liposome is a tiny bubble (vesicle), made up of lipids. Liposomes can be used as drug delivery carriers to transport relatively toxic drugs into diseased cells, where they can exert their maximum effect. DNA molecules may also be entrapped in, or bound to the surface of, the vesicles, and subsequent fusion of the liposome with the cell membrane will deliver the DNA into the cell.

Logic-gates
A logic gate is an elementary building block of a digital circuit. Most logic gates have two inputs and one output.

Metabolic engineering
Metabolic engineering is the science that combines systematic analysis of metabolic and other pathways with molecular biological techniques to improve cellular properties by designing and implementing rational genetic modifications.

Metabolic flux
A term used in metabolic analysis to indicate the rate of a multi-component system (metabolic pathway), while "rate" is reserved for individual components (enzyme).

Metabolic pathway
Metabolic pathways are series of chemical reactions occurring in a cell. In each pathway, a principal chemical is modified by a series of chemical reactions.

Metabolite
Any substance produced by metabolism or by a metabolic process. Any substance involved in metabolism (either as a product of metabolism or as necessary for metabolism).

Metabolomics
The scientific study of the set of metabolites present within an organism, cell, or tissue.

Micelles
Micelles are spherical aggregates of surfactant molecules that form in aqueous solutions. This phenomenon, for example, occurs in soaps and detergents.

Microbe
Microbes are single-cell organisms.

Microorganism
Microorganisms are microscopic organisms, especially bacteria, viruses and fungi.

Monoclonal antibodies
Antibodies are molecules that mediate a number of immunological functions by identifying and binding to 'foreign' objects (e.g. proteins, small molecules, bacteria).

A monoclonal antibody refers to a preparation of antibodies in which all the material is a single protein sequence (a single clone).

Nanocapsules
A nanocapsule is any nanoparticle that consists of a shell and a space, in which desired substances may be contained.

Nanocarriers
Nanocarriers are colloidal particulate systems with size ranging between 10-1000 nm that can be used to encapsulate chemical substitutes and deliver them to cells.

Nanoemulsions
Nanoemulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm.

Nanoparticles
Nanoparticles are particles of less than 100 nm in diameter that exhibit new or enhanced size-dependent properties compared with larger particles of the same material.

Nanospheres
Polymeric nanospheres can be simply defined as latex particles in nanoscale that are synthesised by polymerisation or emulsification processes.

Neuro-transmitter
A chemical substance which is released at the end of a nerve fibre by the arrival of a nerve impulse and, by diffusing across the synapse or junction, effects the transfer of the impulse to another nerve fibre, a muscle fibre, or some other structure.

Nucleoside
A nitrogenous base (purine or pyrimidine) bound to a pentose sugar ribose (RNA nucleoside) or deoxyribose (DNA nucleoside).

Nucleotide
A compound consisting of a nucleoside linked to a phosphate group. Nucleotides form the basic structural unit of nucleic acids such as DNA and RNA.

Olfactory processes
Processes involved in odour perception.

Oscillators
An oscillator is a mechanical or electronic device that works on the principles of oscillation: a periodic fluctuation between two things based on changes in energy. Computers, clocks, watches, radios, and metal detectors are among the many devices that use oscillators.

Peptide
A peptide is a compound consisting of two or more amino acids linked in a chain by an amide bond formed from the carboxyl group of one amino acid with the amino group of the other.

Phosphotriesterase (PTE)
Phosphotriesterase from *Pseudomonas diminuta* (PTE) is an extremely efficient metalloenzyme that hydrolyses organo-phosphorous compounds (this can include some nerve agents).

Phosphorylation
The process of adding a phosphate moiety to a biological molecule (to prepare a phosphorylated molecule).

Plasmids
A genetic structure in a cell that can replicate independently of the chromosomes, typically a small circular DNA strand in the cytoplasm of a bacterium or protozoan. Plasmids are much used in the laboratory manipulation of genes.

Proteins
Large biological molecules composed of one or more long chains of amino acids that are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, etc., and as enzymes and antibodies.

Proteomics
Proteomics studies the structure and function of proteins, the principal constituents of the protoplasm of all cells.

PSF Chemicals
These are chemicals that contain any of the elements: phosphorous, sulfur and fluorine.

Rational design
The use of computational methods to predict which amino acid sequences will produce proteins with specific properties.

Receptor
A receptor is a protein molecule, embedded in either the plasma membrane or cytoplasm of a cell, to which a mobile signaling (or "signal") molecule may attach.

Recombinant DNA
The result of combining DNA fragments from different sources. Recombinant DNA techniques are widely used to manipulate DNA, including: the identification and cloning of genes; the study of the expression of cloned genes; and the production of large quantities of gene products.

Recombinant protein
Proteins that result from the expression of recombinant DNA within living cells are termed recombinant proteins.

RNA
A nucleic acid that is generally single stranded (double stranded in some viruses) and plays a role in transferring information from DNA to the protein-forming system of the cell.

Scheduled chemicals
These are chemicals that are listed in schedules 1, 2 or 3 under the Chemical Weapons Convention.

shRNA
A small hairpin RNA that can silence gene expression.

Enantiomers
Enantiomers are molecules that can exist in two forms which are mirror images of one another. The individual forms are often denoted as Rp or Sp to distinguish them from one another.

Stoichiometric
The quantitative relationship between reactants and products in a chemical reaction.

Systems biology
Systems biology is the study of systems of biological components, which may be molecules, cells, organisms or entire species.

TALENs
The newly-developed transcription activator-like effector nucleases (TALENs) comprise a nonspecific DNA-cleaving nuclease fused to a DNA-binding domain that can be easily engineered so that TALENs can target essentially any sequence.

Transcriptome
A transcriptome is a collection of all the transcripts present in a given cell.

Transcriptomics
The study of the complete set of RNAs (transcriptome) encoded by the genome of a specific cell or organism at a specific time or under a specific set of conditions.

Transducer
Biological transducers translate physical or chemical stimuli into electrical or chemical signals which can be processed by the organism.

Transgenic
This is used to mean organisms that have had genes from other species inserted into their genome.

Zinc finger nucleases
A class of DNA-binding proteins that facilitate genome editing by creating a double-stranded break in DNA at a user-specified location.

Vesicles
Miniscule membrane-enclosed sacs within a cell or organelles of a eukaryotic cell. These sacs help transport or absorb proteins, enzymes and other molecules involved in cellular processes.

Viral capsid
The protective protein coat that surrounds a virus. The capsid often determines the shape of the virus.

Annexes:

Annex 1: Temporary Working Group on the Convergence of Chemistry and Biology Terms of Reference

Annex 2: Temporary Working Group on the Convergence of Chemistry and Biology Participants

Annex 1

TEMPORARY WORKING GROUP ON THE CONVERGENCE OF CHEMISTRY AND BIOLOGY TERMS OF REFERENCE[66]

1) The objective of the temporary working group (TWG) on the convergence of chemistry and biology is to further explore this convergence and the potential implications for the implementation of the Chemical Weapons Convention (CWC), as recommended by the Scientific Advisory Board (SAB) at its Sixteenth Session (see paragraph 14.3 of SAB-16/1, dated 6 April 2011). The Director-General endorsed this recommendation and, in accordance with paragraph 9 of the terms of reference of the SAB, established the working group and appointed Dr Robert Mathews as the Chair of the TWG. The first meeting was held in November 2011. After Dr Mathews had finished his term on the SAB in 2011, the Director-General appointed Mr Bill Kane as the new Chair of the TWG.

2) The TWG should consist of individuals with expertise in: chemistry; biotechnology and biological sciences; relevant research; relevant commercial/industrial production; and trends in other relevant scientific disciplines. Qualified members of the Scientific Advisory Board may join the TWG. Members of relevant international scientific organisations and key scientific unions in the life sciences, and international organisations may also be invited to join the group. Guest speakers may be invited from time to time. The TWG may also, when necessary, draw upon the expertise of the Technical Secretariat.

3) The TWG should consider both risks and benefits to the implementation of the CWC that arise from the convergence of the sciences. The TWG will report to the Scientific Advisory Board on:

    a. Biologically mediated synthesis of chemicals:

        i. The processes that are used in the biologically mediated synthesis of chemicals;

        ii. The extent of use of biologically mediated synthesis in commercial chemical production;

        iii. The use of biologically mediated techniques for the synthesis of toxic chemicals;

[66]Version 2, 22 June 2012, as approved by the Director-General of the OPCW. Version 1 was approved on 23 May 2011.

iv. The application of biologically mediated processes for the synthesis/production of toxins and bioregulators, and future trends;

b. Chemical synthesis of agents of biological origin (e.g. toxins, bioregulators) and of replicating systems;

c. Whether any biotechnological processes exist, other than biologically mediated synthesis, that are of relevance to the implementation of the CWC; (i.e. whether the types of production equipment and processes may pose a significant risk to the object and purpose of the Convention);

d. The meaning of "production by synthesis";

e. The potential benefits to the CWC of the convergence of chemistry and biology (which might include e.g. protective measures, medical countermeasures, and diagnostics);

f. Whether there are other scientific disciplines, apart from biology, that are converging in a significant way with chemistry, and whether it is possible to identify triggers or early-warning indicators for potential game-changing events that might have implications (whether positive or negative) for the CWC.

4) The temporary working group will also advise on how to bring together expertise on the Biological Weapons Convention and Chemical Weapons Convention in order to discuss areas of common interest between the two Conventions and share knowledge related to convergence.

5) The temporary working group will exist for a period of two years from the date of its first Meeting, at which time its work will be reviewed by the SAB and the Director-General, and a decision will be made as to whether it should continue its work, and whether the Terms of Reference should be further revised.

Annex 2

TEMPORARY WORKING GROUP
ON THE CONVERGENCE OF CHEMISTRY AND BIOLOGY PARTICIPANTS

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[67]*	Consultant of Monsanto Company, United States of America
Professor Hua Li	Chinese Academy of Military Medical Sciences, China
Dr. Robert Mathews[68]*	Defence Science and Technology Organisation, Melbourne, Australia
Dr. Piers D. Millet	United Nations
Mr. Stefan Mogl*	Spiez Laboratory, Switzerland
Dr. William D. Provine	DuPont Central Research & Development, United States of America
Professor Igor Rybalchenko*	Military Science Centre of the Ministry of Defence, Moscow, Russian federation
Professor Alejandra Graciela Suárez[69]*	Universidad Nacional de Rosario, Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina
Dr. Muhammad Zafar-Uz-Zaman*	National Engineering and Scientific Commission (NESCOM), Islamabad, Pakistan
Dr. Joel Cherry (guest speaker, Third Meeting)	Amyris Biotechnologies, Emeryville, United States of America
Richard Johnson (guest speaker, Second Meeting)	Global Helix LLC, United States of America
Professor Scott Mohr (guest speaker, Second, Third and Fourth Meetings)	Bioinformatics Graduate Program and the Department of Chemistry, Boston University, United States of America
Pieter van Boheemen (guest speaker, Second Meeting)	Dutch DIY Bio community, The Netherlands

* Members of the SAB during all or part of the period of existence of the TWG

[67] Chairman of the TWG on the Convergence of Chemistry and Biology from the Second Meeting onward.
[68] Chairman of the TWG on the Convergence of Chemistry and Biology from the First Meeting until 23 November 2011.
[69] Joined at Fourth Meeting after becoming Chair of the SAB.

Convergence of Chemistry and Biology

Report of the Scientific Advisory Board's Temporary Working Group

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