

禁止化学武器组织



ORGANISATION FOR The prohibition of Chemical weapons



ОРГАНИЗАЦИЯ ПО Запрещению химического оружия



ORGANISATION POUR L'INTERDICTION Des Armes chimiques







Presented to Side event for Conference of States Parties 21 28 November 2017

Cheng Tang Vice Chairperson, the Scientific Advisory Board





Plan

- Summary of the Workshop on Trends in Chemical Production (Cheng Tang)
 - Experiments of making ice creams (Chris, Jonathan, Siqing and Amy)
 - ✓ Science ABC relevant to the experiment
 - Outcomes of the workshop
- Conclusions and the future plan (Jonathan Forman)
 - >Additional ice cream test & observations
 - Road map towards the Fourth Review Conference

International Workshop on Trends in Chemical

Production

3-5 October 2017, Zagreb, Croatia

Institut za medicinska istraživanja i medicinu rada

ut za Institute cinska | for Medical živanja Research and dicinu Occupational Health

Funded by



Under the auspices of the Croatia President Kolinda Grabar-Kitarović







4





of a series intended to the 4TH RevCom

Mr Mario Antonić

State Secretary Ministry of Economy, Entrepreneurship and Crafts of Croatia

"achievements in the field of chemistry should be exclusively used to the benefit of humans in a manner not forbidden by the Convention, by means of promoting free trade in chemical"



Overview workshop sessions and discussions

Trends in chemical production



Examined trends in all sectors of the chemical industry

Chemical economy Commodity chemicals Pharmaceuticals Fine/speciality chemicals Custom automated synthesis Proteins and nucleic acids Agricultural chemicals Regulatory issues

The workshop discussed in 10 different sessions:

Chemical Industry and the Chemical Weapons Convention

Mr Cheng Tang (OPCW SAB Vice-Chairperson), Moderator





Trends in the European and global chemical industry (Dr *René van Sloten, cefic*)



Industry inspections and Chemical Weapons Convention policy: looking toward the future (Dr Stephanie Dare-Doyen, OPCW Office of Strategy and Policy)

Commodity and Platform Chemicals

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Professor Ferruccio Trifiró (OPCW SAB), Moderator



Future directions of the modern chemical industry (*Professor Fabrizio Cavani, University of Bologna*)



Sustainability in Chemistry (Dr Detlef Maennig, Evonik Industries AG)



Chemical production by conversion of carbon to products through gas fermentation (*Dr Sean Simpson, LanzaTech*)

Bio-based Production

Professor Isel Alonso (OPCW SAB), Moderator





Manufacturing: current status and future of biologicals in therapy (Dr Florian M. Wurm, ExcellGene SA)



European bio based industries sector (Mr Andrea Božić, Saponia)

Specialty and Fine Chemicals, and Small Scale Production

Dr Koji Takeuchi (OPCW SAB), Moderator





Fine chemicals – current trends and challenges in industry (*Dr Olaf Burkhardt, Evonik Industries AG*)



Custom synthesis in chemical production (Dr Tony Bastock, Contract Chemicals UK)



Trends in bioproduction and bioreactor design in relation to specialty chemical production (*Dr i.r. Nico M.G. Oosterhuis, Director of Technology, Celltainer Biotech BV*)

Pharmaceuticals

Dr Renate Becker-Arnold (OPCW SAB), Moderator





Highly active pharmaceutical ingredients (Dr Andreas Beyeler, F. Hoffmann-La Roche AG)



Safety and quality by design: minimizing risk and environmental impact in pharmaceutical production (Dr Ernest Meštrović, Teva Group)

Agricultural Chemicals Ms Barbara Hedler (OPCW Industry Verification Branch), Moderator



Pesticides (Dr Syed Raza, OPCW SAB)

Synthesis Tools

Dr Christophe Curty (OPCW SAB), Moderator





Dial-a-Molecule (Professor Richard Whitby, University of Southampton)



Continuous flow reactor technology (Dr Kerry Gimore, Max Planck Institute of Colloids and Interfaces)

Nucleic Acids

Dr Pål Aas (OPCW SAB), Moderator





Next-generation DNA synthesis: a biological tool driving innovation in metabolic engineering (Dr Devin Leake, Ginko Bioworks)



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Chemical Analysis and Informatics Professor Roberto Martínez-Álvarez (OPCW SAB), Moderator





Transferable learnings from a decade of mutagenic impurity analysis (Dr Dave Elder, CMC Consultant)



Machine learning in chemical synthesis (Dr Marwin Segler, Westfälische-Wilhelms Universität Münster)

Regulatory Frameworks

Dr Stephanie Dare-Doyen (OPCW Office of Strategy and Policy), Moderator



Regulation in the chemical industry (Dr Renate Becker-Arnold, OPCW SAB)



Biomediated processes and industry verification under the Chemical Weapons Convention (*Ms Barbara Hedler, OPCW Industry Verification Branch*)

Highlights of the trend of chemical production and the implementation of CWC



Trends in the European and global chemical industry

- Dr René van Sloten from cefic (Europe Chemical Industry Council) discussed the evolution of chemical production after entry into force of the Convention.
 - 1997 as "tripolar", with the European Union (EU), the United States of America (USA), and Japan as the top three chemical producing regions;
 - The world has since witnessed the emergence of multiple new production platforms in Brazil, India, the Middle East, South East Asia, and Korea. Roughly 40% of world chemical production now occurs in China.



Trends in the European and global chemical industry

 Dr Ren Industr product

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EU chemicals sales increase by nearly 60% in 20 years, while its world market share halves

EU share of global chemicals market



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World landscape of the chemical industry is changing rapidly





NEW MANUFACTURING PROJECTS ARE GROWING OUR ECONOMY & CREATING JOBS



"13th Five-Year Plan"

- From "following the lead" to "taking the lead" and from a big country of petroleum and chemical industry to a "great power"
 - Leading on technology innovation and trade
 Prevailing in international
 - Prevailing in international markets Page 7

World landscape of the chemical industry is changing rapidly





NEW MANUFACTURING PROJECTS ARE

13th Five-Year PlanFrom "following the lead"

➤A shale gas boom has revived the chemical industry in the USA;

EU chemical industry are seeking to move up the innovation ladder by developing products that provide solutions to global challenges that include climate change, energy, water, health, and food.





Experiment I: Liquid Nitrogen Ice Cream Preparation

- Background: The workshop discussed production of chemicals in large scales ... liquid nitrogen ice cream preparation is very much like the process of an industry scale production of chemicals with different raw materials ...
- <u>Science ABC</u>: Examples of large scale industry production of chemicals
- <u>Action now</u>: A team work ... Assitance with Chris, Jonathan, Siqing & Amy

Future directions of the modern chemical industry

Fabrizio Cavani

Dipartimento di Chimica Industriale "Toso Montanari", ALAM MATER STUDIORUM Università di Bologna





Future directions of the modern chemical industry

Chemicals represent one of the largest and most research and development (R&D) intensive manufacturing sectors in all of the advanced economies, whose patterns of innovation can profoundly impact economic growth;

highlighted some areas of significant change occurring in the European chemical industry with the aim of lowering environmental impact, while maintaining competitiveness





The new Sustainability Paradigma: Replacement of fossil-derived building blocks with renewable raw materials



Conclusions

The chemical industry is facing important challenges, and is now committed at maintaining the **competitiveness** but also at improving its **environmental performance**

One of the most important target is the replacement of fossilbased raw materials with **renewable-based building blocks** (bioplatform molecules). The main issue here is the **economic sustainability**. The **co-location** model may help in achieving substantial savings of investments.

However, also the **environmental sustainability** has to be carefully evaluated, since a truly better performance can be achieved only under specific conditions.



Sustainability in Chemical Industry

Dr. Detlef Maennig OPCW Workshop on Trends in Chemical Production Zagreb, Croatia, October 3 – 5, 2017





Responsible Care®





Sustainability is not a fashion or a marketing gimmick, let alone a cost driver. It is a driver for innovation, profitability and social progress. Why is that so?







Global Product Strategy



OPCW

Organisation for the Prohibition of Chemical Weapons



1997- <mark>20</mark>17

Industry inspections and Chemical Weapons Convention Policy: looking toward the future

> Dr Stephanie Daré Doyen OPCW Office of Strategy and Policy

(data from 2015 OPCW Annual Report)



Article VI Inspections – Overview (up to 31 August 2017)

Facilities/Sites By Type	SPs with Declared Facilities	Declared Facilities/Sites	Inspectable Facilities/ Sites	Inspections Conducted since EIF	Inspection days since EIF
Schedule 1	23	26	26	288	4,955
Schedule 2	36	492	201	810	18,893
Schedule 3	35	402	362	468	7,169
OCPF	80	4,299	4,128	1,932	24,120
Total		5,219	4,717	3,498	55,137

A total of 3,498 industry inspections was conducted until 31 August 2017 and over 55,100 days spent on-site by our inspectors.



Adapting to changing realities





Emerging questions

2. Each State Party shall ...ensure that toxic chemicals and their precursors are only developed, produced, ...or used ... for purposes not prohibited under this Convention. To this end, and in order to verify that activities are in accordance with obligations under this Convention, each State Party shall subject S1, S2, S3....other facilities ... to verification measures as provided in the Verification Annex.

- In light of new threats, having in mind the provisions of Article VI, what should be the focus of the inspections?
 - Only declared activities / scheduled chemicals?
 - Or all toxic chemicals in the plant site?



www.opcv



Science ABC related to the large scale industry production of chemicals

TRENDS IN BIOPRODUCTION AND BIOREACTOR DESIGN IN RELATION TO PRODUCTION OF SPECIALTY CHEMICALS



Dr. Ir. Nico Oosterhuis CTO – Celltainer Biotech BV, The Netherlands

Zagreb, October 3rd, 2017





Example of producing bio-based chemicals

Technologies / unit operations

UPSTREAM	DOWNSTREAM	REACTION / FORMU- LATION	
Mixing raw materials Sterilization	Cell separation (filtration, centrifugation, sedimentation)	Reaction (enzymatic, catalytic)	
Fermentation	Purification (crystallization, filtration, chromatography, IX, etc.)	Concentration (filtration, spray-drying, etc.)	
	Concentration (filtration, spray-drying, etc.)		

Process lay-out example

(biocatalysis of ferulic acid to vanillin by Streptomyces sp., Givaudan)







Typical fermentation factories



Biopharmaceuticals




Requirements to run a fermentation process Starch Sugar Raw materials Cellulose Gene technology Carbohydrates Fermentation equipment (up to large scale) Glycerol DSP equipment Process and fermentation knowledge Sterility engineering Operational excellence

Lysine production process



Lysine – factory under construction (Russia)











Microbial: not only STR



Evolution of bioreactor and its trends / developments

Cell culture bioreactors







Vaccine production (verocells), Sanofi-Pasteur, 1985



Stirred bioreactor - most commonly used



Improved mixing Less energy Higher mass transfer Low shear *Combinations*



Bioreactor trends

Large-scale bioreactors

special stirrer designs / combinations

Single-use

- No cleaning (validation)
- Less infrastructure
- Sterility guarantee

Continuous processing => smaller bioreactors

- Perfusion high cell density / volumetric productivity
- Micro-carriers new (dissolving) materials
- Instrumentation
 - Better level of process control
 - More in-line / difficult for single-use
 - Model based process control

Dedicated facilties

Smaller reactors

Biopharmaceuticals

- All based on gene technologies
- Produced in multi-purpose installations
- Dedicated purification processes

AND:

- Introduction of single-use equipment makes installations more versatile
- Installations can be used for production of:
 - Toxins
 - Viruses
 - Modified bacteria / viruses
 - Etc.

Single-use bioreactors





SAFETY

- Pre-sterilized
- No contamination

COSTS

- No cleaning
- Simple infrastructure
- Lower maintenance

REQUIREMENTS

- Equipment
- Bags
- Components
- Clean room(s)
- Experience

Experiment II: Making ice cream in a small plastic bag

- <u>Background</u>: the workshop discussed disposable bioreactors ...making ice cream in a small palstic bag is very much like the approach producing chemcials in disposable bioreactors ...
- <u>Science ABC</u>: Evolution of bioreactor and its trends
 / developments
- <u>Action now</u>: making ice cream in a small plastic bag.... Assistance with Chris, Jonathan, Siqing & Amy

Type of single-use bioreactors



Biotoxin production: requirements

- (Single-use) bioreactor
- Simple laboratory
- Micro-organism + process
- Simple filtration or purification (crystallization)

Product	Production strain	Process
Dysport [®]	Hall	Fermentation Dialysis Chronatography
Azzalure®	Hall	Fermentation Dialysis Chromatography
Botox ⁸	Allergan "hyper"	Fermentation Precipitation "Crystallisation"
Vistabel [®] & Vistabex [®]	Allergan "hyper"	Fermerization Precipitation "Crystallisation"
Xeomin®	Hall	[Unpublished]
Bocouture [®]	Hall	[Unpublished]









Conclusions in relation to (bio)chemical weapons

LARGE SCALE PROCESSES

- Fermentation processes are very dedicated
- Raw material position required
- Capital and energy intensive productions
- Bio-building blocks to be used for further chemical modifications

SMALL SCALE PROCESSES

- Introduction of single-use technologies: less infrastructure required
- Limited number of technology suppliers (US/Europe)
- Installations too small for production of chemical weapons
- Avaibalilty of genetic modification techniques
- Production of bio-toxins / viruses / bacteria becomes more easy



THE ROLE OF CUSTOM SYNTHESIS IN THE CHEMICAL INDUSTRY





Dr Tony Bastock

Chairman Contract Chemicals Ltd Vice President Cefic

Contract Chemicals Company Profile

- established in1977
- privately owned
- turnover ca. €30m per annum
- sales in over 40 countries
- employ around 100 people
- based in Knowsley, UK



Contract Chemicals

CMO's - Custom, Toll, Contract Manufacture

- •CMO: Custom/Contract Manufacturing Organisation
- Custom manufacturing:

the process of making products or product lines to a customer's unique specifications.

•Toll Manufacturing:

the process of a company providing its raw materials or semi-finished goods to a third-party CMO who often has specialized equipment or chemistry, to carry manufacturing processes on its behalf using those materials or goods for a fee or toll.

Contract Manufacturing:

either of the above, with a term/conditions contract in place



CMO's - Custom, Toll, Controct Manufacture

- •CMO: Custom/Contract Manufacturing
- •Custom manufacturing:

the process of making product lines to a custr specifications.

•Toll Manufacturing:

te

the process semi-fip: has its raw materials or ty CMO who often emistry, to carry ts behalf using those or toll.



ns contract in place

•Cont

The Need for Contract Manufacture

The customer company:-

- fills its capacity, but needs more product
- develops a new product and wants to test the market before investing in a new plant
- does not have the equipment and/or chemistry to produce a new product
- wants to outsource early stages, but produce the final compound in-house
- wants local production for local markets
- needs building blocks (intermediates) for its products or formulations manufactured to bespoke specifications

Choosing a CMO



- Wow, we need to sign a non-disclosure agreement to attend the office Christmas party this year!
- Every chemical company is a CMO!
- Almost every toll manufacturing process is carried out under a non-disclosure agreement
 - -These can be onerous and restrictive
- Choose a company whose equipment, chemistry and regulatory position fits the process/product



-Large amounts of information available through Web, trade shows, trade press and company literature

Be prepared to invest



Chemical Weapons Manufacture



Chemical Weapons Manufacture



Thematic Discussions: four topics considered





Interactive Discussions





Topic 1:

Advances in chemical production technologies and the synthesis of chemicals scheduled under the Chemical Weapons Convention Facilitated by Jonathan Forman

- What has changed and what impact might it have on recognizing a relevant process?
- If the answer changes when considering different production scales?



Topic 2:

Advances in biological production technologies and the synthesis of bioregulators and/or biological toxins Facilitated by Cheng Tang

- What is the current status of the chemical synthesis of bioregulators and/or biological toxins?
- Is there an impact to the Chemical Weapons Convention given the capabilities available for production of bioregulators and/or toxins?



Topic 3:

New synthesis tools and technologies for enhancing the capabilities of the OPCW Designated Laboratories Facilitated by Chris Timperley

- What synthetic tools and methods are available for enhancing the capabilities of OPCW Designated Labs?
- And which synthetic technologies being adopted in academia and/or industry could benefit the Designated Labs?



Topic 4:

The impact of current trends and future directions in chemical production on the Chemical Weapons Convention verification regime Facilitated by Stephanie Dare-Doyen

- Which current trends and potential future directions in chemical production would be of concern for the Convention?
- In light of advances in science and technology, and a changing security environment, are revisions to the verification approach necessary?

The Final Report (SAB-26/WP.2) (REPORT OF THE SCIENTIFIC ADVISORY BOARD'S WORKSHOP ON TRENDS IN CHEMICAL PRODUCTION)

ОРСЖ	Scientific Advisory Board
Twenty-Sixth Session 16 – 20 October 2017	SAB-26/WP.2 19 October 2017 ENGLISH only
REPORT OF THE SO ON TREM	IENTIFIC ADVISORY BOARD'S WORKSHOP
1. EXECUTIVE SUMMAR	RY
1.1 The OPCW Scientific A. Medical Research and Workshop on Trends in C the Republic of Crostin. ² organized under the aunpo Ministry of Economy, End fourth and final workshop developments in science Chemical Weapons Con December 2018.	dvisory Board (SAB) in cooperation with the Institute of Occupational Health (IMROH) held an "International Ibamical Production", from 3 to 5 October 2017 in Zagreb, "The workshop was funded by the European Union" and ces of the Croatian President Kolinda Graben-Kitzaović, the trepreneurship and Crafts; and the City of Zagreb. It was the p of a senies" intended to inform the report of the SAB on and technology to the Fourth Review Conference" of the avention (hereinafter, "the Convention") to be held in
1.2 The past 70 years has a impact from the field of found). ⁶ Chemistry itself evolving into an area of a	seen extraordinary intellectual growth and socioeconomic chamistry (with both positive and negative examples to be 'has experienced continual change throughout its history, cience that provides significant opportunities for addressing
 For additional information on I OPCW Scientific Advisory B Production, 9 October 2017 	MROH, see <u>https://www.imi.lo/on/</u> teed Reviews Technological Developments and Trends in Chemical 7, www.speer.org/news/schelus/powester/file-advisory-board-preimse-
3 Inchnological-developmenta-an This funding was provided they in Science and Technology) of	<u>Advantation in a production</u> righ Project III (Science and Technology: Assessment of Developments EU Connell Decision (CP8P) 2015/259 dated 17 February 2015.
 The fire previous workshops and the Potential Applications 22 June 2016 in Hell work open of Mindmin (JCC Taxisity, Ramganey Response Paris, France (SAR-24WPZ, 22-24-2027 and 10) " 5 July 2017 in Rio de work open on Mindmin (JCC Fourth Spacial Samion of the C Waspoor Conversion, Change deministry), G. M. 	Contract A Contract Microsoft A., 2015;MARADA (2015) (2015) Contract A., 2015, Contract G.A.B.(25: WPL), deted 1.4 July 2016, WISA (Proceeding Contract Annual Contract Annual Contract Con
CS-2017-0632(E) distributed 25/10/201	

The Final Report (SAB-26/WP.2) (REPORT OF THE SCIENTIFIC ADVISORY BOARD'S WORKSHOP ON TRENDS IN CHEMICAL PRODUCTION)



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

Available in the OPCW webpage https://www.opcw.org/fileadmin/OPCW/SAB/en/ sab-26-wp02_e_.pdf

For additional information on IMROFI, sor: <u>https://www.imi.br/m/</u>

- ² OPCW Scientific Advisory Board Reviews Technological Developments and Trends in Chemical Production, 9 October 2017, <u>www.cpcw.cpcw.cpchwww.cpckalogicw-scientific-advisory-board-sciencetechnological-developments-advisor-development-andvisory</u>.
- ³ This funding was provided through Project III (Science and Technology: Assessment of Developments in Science and Technology) of EU Council Decision (CPRP) 2015/259 dated 17 February 2015, http://www.ew.assessment.aste.accentENPTCTCTrustrations.com/10.1016/00.1016/00.1020

The first previous workshops of the action were: (1) "Chemical Formation Capabilities across the Field and the Potential Applications in Chemical Wargene Convention Implemention", bulk from 20 to 22 Jane 2016 in Helsinki, Finland (SAB/24-WP.1, dated 14 July 2016, hereinagene applications/CC/2004/Dimension/2004/01_a.g.pdf) (2) "Chemical Warflee Agentic Toxicity, Immegracy Response and Medical Convirtamentaries", held from 26 to 27 September 2016 in Paris, France (SAB-24/WP.2, dated 14 October 2016, www.epper.application://CW/3AB/2004/P.2, 224-922, a.p.tf). And (0) "Introvitive Technologies for Chemical Security", held from 3 to 5 July 2017 in Rio de Janezie, Brandi (SAB-26/WP.1, dated 21 July 2017, wron.exee.org/Endminic/CV/WSAB/Benedic/2004/01, SAB-26/

⁵ Fourth Special Samion of the Conference of the States Parises to Review the Operation of the Chemical Weapons Convention.

⁶ Reinverting chemistry; G. M. Whitesides; Augest Chem. Int. Ed.; 2015, 54, 3196 – 3209. DOI: 10.1002/anie.201410684.

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Summary outcomes of the workshop

Outcomes of the workshop

- A fit-for-purpose verification regime should maintain up to date operational knowledge of chemical (and biological) production methods (including aspects of synthesis and analysis).
- b) Drew attention to previous advice from the SAB's temporary working group (TWG) on Verification that considered risk-benefit approaches as a means to focus verification, including consideration of relevant chemicals not on the current schedules.
- c) Recognized a number of areas with potentially transferable learnings from industrial practices. These include approaches to trace analysis and tools for chemical risk assessment.

Outcomes of the workshop (continue)

- d) Several significant developments in the global chemical industry observed over the past 20 years were not recognized until they actually took shape (e.g. they were unanticipated in the years just before they happened).
- e) Synthesis tools being developed for chemical discovery purposes (complemented with machine learning approaches for predicting chemistry) can potentially enable capabilities for laboratories to quickly generate large sets of analytical data, screen for reactivity and toxicity properties, and elucidate degradation pathways of a broad range of chemical classes.

Outcomes of the workshop (continue)

- f) The technical presentations and content of the workshop served as a reminder of the highly trans-disciplinary (convergent) nature of 21st century technology development, with scientific disciplinary convergence going well beyond the fields of chemistry and biology. Sharing of experience on science advice with other relevant disarmament communities (especially the Biological Weapons Convention stakeholders) should be encouraged.
- g) In the discussion of changing realities and the relevance of current verification practices, it was acknowledged that greater levels of science and technology engagement, and knowledge sharing amongst States Parties could also support

Outcomes of the workshop (continue)

The technical presentations and content of the workshop served as a reminder of the highly trans-disciplinary (convergent) nature of 21st century technology de nt. with scientific disciplinary convergence going the fields of chemistry and biology. science advice with other relation 26 endorse communities (especial stakeholders) stakeholders report and these a the relevance of g) s acknowledged that cechnology engagement, and mongst States Parties could also
The next steps

- The SAB will prepare a report to the Forth Review Conference based on the series of four workshops conducted :
 - Chemical Forensic (Helsinki, June 2016)
 - Medical Countermeasures (Paris, October, 2016)
 - Innovative Technologies for Chemical Security (Rio De Janeiro, July 2017)
 - Trends in Chemical Industry (Zagreb, October 2017)
- Jonathan will explain more...

Thank you for your attention!