OPCW

Scientific Advisory Board

SUMMARY OF THE THIRD MEETING OF THE SCIENTIFIC ADVISORY BOARD'S TEMPORARY WORKING GROUP ON CHEMICAL FORENSICS 25 – 27 SEPTEMBER 2024

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

1.1 The Temporary Working Group (TWG) on Chemical Forensics of the Scientific Advisory Board (SAB) held its third meeting from 25 to 27 September 2024. The meeting was chaired by Dr Anne Bossée on behalf of the SAB, with Dr Simon Ovenden as Vice-Chairperson.

1.2 Dr Bossée opened the third meeting of the TWG by warmly welcoming its members and the external speakers and invited all participants to introduce themselves. A list of participants appears in the Annex to this report. She acknowledged the valuable contributions the presentations of the external speakers bring to the TWG's findings. Dr Bossée then invited the TWG members to provide brief updates on their chemical forensics-related work undertaken since the last TWG meeting.

1.3 As no objections or comments were raised in response to the proposed programme of work during the three days of the meeting, the following agenda was adopted:

1. Opening of the meeting and adoption of the agenda

2. Updates from subgroups[1]

3. Biological traceability and chemical forensics of organophosphorus

4. Aspects of data processing in impurity profiling studies

5. Molecular forensics in biothreat scenarios – Chemical profiling of toxic plant materials containing ricin

6. Discussion on end-of-mandate report

7. Data-driven approaches for the chemical exposure assessment

8. Discussion with the OPCW Declaration Assessment Team

9. Discussion with the OPCW Fact-Finding Mission in Syria

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[1]   While agenda items 2, 11, 12, and 14 were discussed separately during the meeting, they are reported herein under a single agenda item for clarity and to minimise duplication.

10. Discussion with the OPCW Investigation and Identification Team

11. Subgroups 1 and 3 breakout sessions[2]

12. Subgroups 2 and 4 breakout sessions[3]

13. Forensic chemistry: Some applications of chemical profiling

14. Recaps from subgroup leads[4]

15. Closing remarks and any other business

16. Closure of the meeting

2. AGENDA ITEMS TWO, ELEVEN, TWELVE, AND FOURTEEN – Discussions on subgroup topics

2.1 Subgroup 1, led by Dr Crister Åstot, is focusing on the state of the art of chemical forensics, and is considering the areas of batch matching, impurity profiling, synthesis routes, geographical and environmental factors, and isotope ratios. During the intersessional period and throughout the third TWG meeting, Subgroup 1 has been working to determine the chemical forensics tools applicable to investigating the use of a chemical weapon.

2.2 A chemical forensics-based investigation would likely follow confirmation of the use of a chemical weapon by OPCW designated laboratories. The subgroup noted that the chemical profiles of chemical warfare agents could play an important role in forensic investigations by providing evidence that may help to identify the perpetrators of chemical weapons attacks. Chemical profiles of chemical warfare agents may be determined using extrinsic chemical attribution signatures (CAS), such as impurities or additives (organic and inorganic), or intrinsic CAS, such as stable isotope ratios and isomeric ratios. These chemical profiles can be utilised through three distinct approaches, depending on the specific chemical incident under investigation.

2.3 The first approach is sample matching, which involves the comparison of two or more samples with a suspected common origin. This process is a common application of chemical forensics where it is used to link events and seized materials to each other. The CAS in these samples may include traces of starting materials and their contaminants and by-products from synthesis, in addition to stabilisers and other components of a chemical warfare agent sample. These signatures enable the comparison of the chemical profiles. While these traces are typically organic, chemical profiles of inorganic trace elements may also prove useful in sample matching.

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2   See footnote 1.
3   Ibid.
4   Ibid.

2.4   The second approach, precursor-product matching, involves comparing the CAS profile of a precursor with that of its product (i.e., a chemical warfare agent). Extrinsic CAS, such as impurities that remain in the product throughout the synthesis and purification process, may be used for precursor-product profiling. Additionally, intrinsic CAS, such as isotope ratios, have demonstrated utility in this area and warrant further investigation.

2.5   Lastly, chemical profiling can provide information on the probable origin of a chemical warfare agent, as well as its production, storage, and dispersal. This process, known as route sourcing, relies on CAS—such as specific by-products from synthesis or remnants of starting materials—that produce a unique distribution in samples from a particular synthesis route. The subgroup also noted that inorganic CAS, such as trace elements, may help identify the means of storage and/or dispersal.

2.6   Subgroup 1 emphasised that reference data is critical for determining the chemical profiles of classes of chemical warfare agent samples (such as those produced by a specific route). For sample matching, independent reference samples are required to assess variations in chemical profiles. For synthetic route sourcing, reference samples from multiple production routes are used to build classification models.

2.7   The subgroup highlighted that new chemical analysis instrumentation, with improved sensitivity and selectivity, will be key in providing evidence of chemical weapons production or use by identifying scheduled chemicals, their degradation products, and related impurities and by-products. The chemical forensics of chemical weapons is a unique field; while the application of ultra-sensitive methods in other forensics fields is limited due to the presence of chemicals in the environment, this is not the case for scheduled chemical warfare agents. The use of these chemicals is banned and, consequently, there are no background levels present in the environment. Subgroup 1 therefore considers increased sensitivity for trace-level analysis in environmental samples to be a priority.

2.8   The application of non-targeted approaches was also discussed. These approaches were deemed particularly useful for samples where limited information is available to direct the analysis. They may also be leveraged to detect and identify unexpected chemical markers related to storage or dispersion. However, for most chemical profiling approaches, the targeted analytical methods are preferred.

2.9   Led by Dr Grégoire Delaporte, Subgroup 2 is addressing future capabilities, focusing on the impact of artificial intelligence (AI), specifically machine learning (ML) and deep learning, on chemical forensics. One of the objectives of the subgroup during this third meeting of the TWG was to narrow down its specific topics of interest relating to AI/ML, guided by input from Subgroup 1. It was proposed that chemical forensics approaches related to sample and precursor production batch matching and synthesis route determination could be supported by AI/ML methods. It was also proposed that "support functions"—topics not directly related to the source inference of a chemical, but that may still be relevant to analysts in their work—could also be addressed by AI/ML methods. These support functions could include database generation (including data augmentation), prediction of analytical and physico-chemical properties, and data mining. Subgroup 2 members agreed that they should also consider any risks posed by AI/ML in the chemical forensics domain, including proliferation issues and the bypassing of existing regulations on chemical weapons, in addition to any

organisational or technical challenges to the implementation of the AI/ML methods by designated laboratories. A literature review on the application of AI/ML methods in the broader field of forensic science is currently being conducted, and the findings will be instrumental in informing the next phase of the work of Subgroup 2.

2.10   In the second meeting of the TWG, Subgroup 3, led by Ms Ang Lee Hwi, continued with its mandated focus on methods and procedures in chemical forensics, and proposed that confidence-building exercises could be useful not only to build capabilities at participating laboratories, but also to generate data to develop a chemical forensics-related database and to validate standard operating procedures. In the intersessional period, the subgroup considered the criteria that the data would need to meet for inclusion in the database. The subgroup members reviewed scientific publications and subsequently proposed various criteria relating to instrumental analysis, the identification of CAS, and the selection of chemical profiles. They recognised that the set of proposed criteria, such as the components of the quality control mix, may not be entirely suitable from the outset, and should be reviewed and refined as exercises progress.

2.11   Following discussions during the second meeting of the TWG, Subgroup 3 recommended that, in support of the proposed exercises, the synthesis of Schedule 1 chemicals be conducted at the Centre for Chemistry and Technology. This would address the potential concerns around revealing laboratory and, consequently, State Party identities through the unique signatures generated, and the possibility of revealing the synthesis routes of Schedule 1 chemicals. Nevertheless, Subgroup 3 noted that States Parties may also contribute to these syntheses should they wish to do so. The syntheses of Schedule 1 chemicals may not only include different routes, but also elicit variations within a particular route, including reaction conditions, matrices, and production scales, for incorporation into the models and database. Laboratories participating in the confidence-building exercises could receive dilute samples of the Schedule 1 chemicals and guidelines on the sample preparation and analytical methods, as well as the criteria for data inclusion. These laboratories would then be required to provide a list of the CAS and the raw data for further analysis, if required. Subgroup 3 noted the importance of establishing a data management protocol to address any concerns regarding the subsequent use of the data.

2.12   During the breakout sessions, Subgroup 3 members proposed two specific recommendations to maximise the value of the proposed confidence-building exercises. First, they proposed creating dedicated opportunities for laboratories to share their experiences in the exercises, enabling participants to use these insights to refine methodologies and strengthen laboratory capabilities. Second, they recommended forming a validation group tasked with defining specific criteria for data inclusion. This validation group would also curate published scientific literature on CAS to be included as chemical warfare agent signatures in the OPCW Central Analytical Database (OCAD), as well as establish a framework for data management.

2.13   Subgroup 3 also discussed the role of designated laboratories in authentic sample analysis in support of non-routine missions and noted the importance of two-way communication between both parties. Designated laboratories would be able to better support non-routine missions if more information about the purpose of the analysis could be made available. The subgroup members considered strengthening the secrecy

agreement between designated laboratories and the OPCW to allow more information to be shared with these laboratories. They also discussed the pertinence of establishing long-standing arrangements for designated laboratories to provide reach-back to non-routine missions even after the conclusion of an analysis, and the provision of training for non-routine missions in order to share appropriate information without compromising information security and sensitivity.

2.14   Given the requirements of non-routine missions, the subgroup considered how proficiency testing may be adapted: Scenarios and scope of analysis (sensitivity and range of chemicals) could be reviewed, and the proficiency tests could subsequently be redesigned to allow designated laboratories to develop capabilities that can better support the investigations of non-routine missions.

2.15   Subgroup 4, led by Dr Hanna Hakulinen, is focusing on how the chemical forensics capabilities of the OPCW can be enhanced. The subgroup has been exploring potential scenarios and identifying questions about chemical forensics and gaps in the investigative process. These included challenges in preserving incident sites to ensure that chemical forensics sampling may still be performed, the possibility that samples from different sites may match one another, and the identification of the most essential analytical methods after verification. Further, questions about the analytical capabilities of designated laboratories and impurity profiling were also considered.

2.16   The subgroup proposed identifying and exploring ways to raise awareness of chemical forensics among first responders, such as law enforcement and rescue services. Discussions highlighted that establishing a link between first responders and investigators is a critical step in harmonising the response and approach adopted. It also ensures that first responders have a greater understanding of the chemical forensics-related aspects at the scene and the importance of the samples that they may be handling.

2.17   Subgroup 4 also proposed that the proficiency test framework could be re-evaluated and updated. This could include updating the scenarios to ensure they are more realistic, and incorporating samples relevant to chemical forensics into the existing proficiency tests, which could assist in identifying capable laboratories. Analytical methods from the VERIFIN Blue Book could be tested and revised as necessary, and new methods added where relevant. Subgroup 4 discussed the increasing need to develop capabilities to analyse unknown unknowns and potentially develop chemical forensics capabilities to analyse biomedical samples, even if this has proved challenging to date. The subgroup stressed the importance of quality control in chemical forensics, as impurity profiling is strongly dependent on factors like instrument performance.

2.18   Collaborative approaches for more effectively building and developing laboratory capabilities in chemical forensics were discussed, including inter-laboratory teamwork, or even efforts at a regional level. Subgroup members emphasised the importance of confidence-building exercises (such as Icarus[5]) and agreed on the need to leverage them further.

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[5]   Icarus is a sample-matching exercise designed to simulate real-world conditions with realistic forensic questions and it will start in early 2025.

2.19   Subgroup 4 members identified that the recruitment of a data scientist specific to chemical forensics at the OPCW could also enhance capabilities. Development of a chemical forensics database, initially modelled on the OCAD and subsequently augmented, was also proposed.

2.20   Finally, the subgroup noted that increasing communication between designated laboratories and non-routine missions could be beneficial.

3.   AGENDA ITEM THREE – Biological traceability and chemical forensics of organophosphorus

3.1   Dr Hongmei Wang, from the State Key Laboratory of NBC Protection for Civilian, China, described the Laboratory's work exploring potential adducts that may form between proteins and organophosphorus nerve agents (OPNAs), specifically G-type and V-type adducts, providing a data set for tracing exposure to organophosphorus compounds. She noted that albumins, in particular, could serve as important targets for the retrospective verification of exposure to OPNAs. In the first stage of this work, systematic analytical methods for determining in vivo and in vitro OPNA exposure doses and identifying protein adducts were established.[6]

3.2   Using sarin (an OPNA), albumin (a protein), and a rabbit animal model, the minimum in vivo and in vitro doses of OPNAs in whole blood were determined. Following protein purification by agarose gel electrophoresis combined with other methods, and subsequent enzyme digestion, the resultant phosphonylated peptides were analysed by Q-Orbitrap tandem mass spectrometry (MS/MS). The database search engine SEQUEST HT was used for structural attribution. The composition of the phosphonylated peptides was identified and the phosphonylated structures and sites were predicted. This method was found to be suitable for the study of the adduct-forming reaction between OPNAs and proteins.

3.3   Dr Wang noted that during studies of adduct formation between G-type OPNAs and the three proteins human serum albumin, IgG, and haemoglobin, it was determined that G-type agents react with the hydroxyl groups on the tyrosine (Y), lysine (K), and serine (S) amino acid residues. This work further indicated that sarin and cyclosarin seemed to have an affinity for S419, while the other seven OPNAs studied bonded with K414. Analysis of the peptide mixture obtained after albumin digestion revealed that the phosphonylated peptide K414VPQVS419TPTLVEVSR was present in high quantities and could also be isolated from the mixture with ease, making it a potential biomarker for OPNA exposure. Adducts formed between tabun (representing dialkylamine cyanophosphate G-series agents) and human serum albumin led to identification of the main binding sites for the first time.[7] Two peptides were also identified as potential biomarkers for exposure to tabun and its analogues. The V-type agents form two types of protein adducts: phosphorylated and disulfide adducts. They

6   Fu, Feiyan, Runli Gao, Ruihua Zhang, Pengcheng Zhao, Xiaogang Lu, Liqin Li, Hongmei Wang, et al. 2019. "Verification of Soman-Related Nerve Agents via Detection of Phosphonylated Adducts from Rabbit Album in *in Vitro* and *in Vivo*." Archives of Toxicology 93, no. 7: 1853–63. https://doi.org/10.1007/s00204-019-02485-8.

7   Fu, Feiyan, Fengjuan Sun, Xiaogang Lu, Tianyu Song, Junjie Ding, Runli Gao, Hongmei Wang, and Chengxin Pei, 2019. "A Novel Potential Biomarker on Y263 Site in Human Serum Albumin Poisoned by Six Nerve Agents." Journal of Chromatography B 1104: 168–75. https://doi.org/10.1016/j.jchromb.2018.11.011.

bind by reacting with the thiol group of cysteine amino acid residues. Multi-species and multi-source albumins were used to identify a larger number of traceable adducts.[8] Potential biomarkers of exposure to V-type agents were also identified.[9,10] To date, Dr Wang and her team have identified more than 500 peptide fragments, allowing them to develop their bio-adduct database.

3.4   Chemical forensics is another key area of research, with focus initially on attribution of the synthesis routes of tabun and its analogues. The synthesis routes of *N*,*N*-dimethylaminophosphoryl dichloride—the principal tabun precursor—were examined and, based on cost and availability of starting materials, three of five possible routes were selected for further study. A total of 27 samples were synthesised and analysed by nuclear magnetic resonance (NMR) spectroscopy and gas chromatography-mass spectrometry (GC-MS). The chemical attribution signatures were identified in the GC-MS data and their chemical structures were confirmed by comparison with data from the National Institute of Standards and Technology (NIST) and the OCAD. Each synthetic route gave rise to a unique chemical attribution signature profile. Prior to analysis, the samples underwent hydrolytic acidification, as this produces characteristic information on the compounds and is conducive to constructing classification and prediction models. Analysis and mining this characteristic information enabled the different synthesis routes to be identified. Some amino species generated as by-products during synthesis of the precursors remained unchanged during the synthesis of tabun. Given their stability, they could also be used as markers to identify the synthesis route used.

3.5   Finally, Dr Wang discussed the potential application of terahertz spectroscopy in chemical forensics, highlighting its ability to significantly reduce sample analysis time, compared to current techniques like mass spectrometry and NMR spectroscopy.

3.6   Following this, TWG members discussed several elements of Dr Wang's presentation, such as sampling guidelines, development of the tabun matrix and the associated criteria, the purification of fragments, and the length of time post-exposure that peptide markers remain detectable. Regarding exposure to an unknown substance, Dr Wang confirmed that her team's database of 500+ peptide fragments could be used to identify the chemical in question.

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[8]   Wang, Jin, Meng Jin, Qian Wang, Xiaogang Lu, Runli Gao, Fengxia Sun, Chengxin Pei, and Hongmei Wang. 2024. "Study on Phosphonylation and Modification Characteristics of Organophosphorus Nerve Agents on Multi-Species and Multi-Source Albumins." Journal of Chromatography B 1240 (June): 124155. https://doi.org/10.1016/j.jchromb.2024.124155.

[9]   Fu, Feiyan, Jialin Chen, Pengcheng Zhao, Xiaogang Lu, Runli Gao, Dong Chen, Haibo Liu, Hongmei Wang, and Chengxin Pei, 2020. "Tracing and Attribution of V-Type Nerve Agents in Human Exposure by Strategy of Assessing the Phosphonylated and Disulfide Adducts on Ceruloplasmin." Toxicology 430: 152346. https://doi.org/10.1016/j.tox.2019.152346.

[10]   Wang, Jin, Fengjuan Sun, Xiaogang Lu, Runli Gao, Chengxin Pei, and Hongmei Wang, 2022. "Retrospective Detection for V-Type OPNAs Exposure via Phosphonylation and Disulfide Adducts in Albumin." Scientific Reports 12, no. 1: 10979. https://doi.org/10.1038/s41598-022-15198-3.

4. AGENDA ITEM FOUR – Aspects of data processing in impurity profiling studies

4.1 Dr Karin Höjer Holmgren, from the Swedish Defence Research Agency (FOI), gave an overview of her research in impurity profiling. She outlined the different data processing tools and approaches she uses, as well as how markers are identified. She also shared brief overviews of a few scientific papers relevant to the chemical forensics of chemical weapons.

4.2 Relying on her previous studies on route sourcing, Dr Holmgren emphasised the importance of experiment planning, as well as some challenges regarding samples, such as availability, the difference between laboratory-based samples and authentic samples, and the natural variability across samples of the same type. Dr Holmgren also shared the results of a recent study showing that similar CAS from a sample of methylphosphonic dichloride can be obtained by different analytical laboratories, indicating that consistent, reproducible chemical forensics information is achievable across multiple laboratories. However, despite some promising recent work in this space, there is still a paucity of publications reporting on route differences, batch differences, and sample matching of chemical warfare agents.

4.3 Dr Holmgren warned that even though GC-MS is often applied to the analysis of chemical warfare agents, it presents limitations, since it does not detect all the compounds present in the samples. Furthermore, the use of a targeted or an untargeted analysis depends on the kind of study that is being conducted.

4.4 The use of data processing tools, such as AMDIS, TraceFinder, and Compound Discoverer, is advantageous in chemical forensics applications. These tools are deconvolution programs, assisting researchers to acquire a cleaner spectrum faster than manual work. All have their pros and cons. For example, FOI has used TraceFinder to analyse high-resolution GC-MS data, finding it a flexible program that can be applied in different relevant settings. However, Dr Holmgren also shared some of their difficulties in using the program, including data processing issues and temporal constraints.

4.5 The identification of signatures is one of the principal objectives in chemical forensics. Dr Holmgren described different strategies that can be used, such as spectral library searches or using orthogonal techniques to analyse samples. However, when there are still unidentified signatures then additional factors need to be considered, such as relative abundance, synthetic pathways, or the use of chemometric standards.

4.6 Dr Holmgren then stressed the importance of reference samples and libraries, both of identified forensic markers as well as of reference signatures. Consequently, the knowledge of the behaviours and stability of the stored samples is also necessary. Dr Holmgren finished by emphasising some overarching needs in the field, such as the development of methods for sample matching, improved cooperation between researchers, method validation, and studies covering more classes of chemical warfare agents.

4.7 Members of the TWG commented on and discussed a number of themes mentioned by Dr Holmgren, including the identification of signatures using alignment and gas chromatography–high-resolution mass spectrometry with electron ionisation (GC-HRMS EI), operation in the absence of reference samples, weaknesses found in deconvolution programs, and the possibilities of untargeted and targeted analysis. The

benefits of having validated methods to employ and the possibility of using AI models to validate methods were also discussed. The members highlighted the relevance of the discussion as an opportunity for the designated laboratories to create a shared database of spectral data related to chemical forensics.

5. **AGENDA ITEM FIVE – Molecular forensics in biothreat scenarios – Chemical profiling of toxic plant materials containing ricin**

5.1   Ms Lisa Scharrenbroch, from the Federal Criminal Police Office, Germany, presented ricin-related work that has been conducted as part of the joint German-French PLANT project. In response to the growing threat of bioterrorism in recent years, the PLANT project was established as a collaborative effort between French and German partners. It aims to enhance preparedness for bioterrorism scenarios involving ricin and abrin, including improving on-site detection and laboratory-based identification methods, and developing a comprehensive molecular forensics capability.

5.2   Analytical methods for the detection of ricin have already been established, but supplementary molecular forensic analysis is crucial to link different pieces of evidence to a common source or toxin extraction process, and this is highly challenging for complex biological samples. To raise the evidential value of forensic investigations in this field, orthogonal methods and chemometric models have been developed and evaluated according to their potential to retrospectively categorise toxin-containing pieces of evidence.

5.3   Biomolecular compositions of crude castor seeds from the *Ricinus communis* (*R. communis*) plant and purified ricin materials were characterised in a proof-of-principle study combining metabolomic and lipidomic approaches. Ms Scharrenbroch explained that sample preparation was performed using known procedures, and orthogonal analytical methods were based on untargeted reversed-phase liquid chromatography coupled to high-resolution mass spectrometry (RP-LC-HRMS), isotope ratio mass spectrometry (IRMS), and NMR spectroscopy.

5.4   The untargeted liquid chromatography high-resolution Fourier transform mass spectrometry (LC-HR-FTMS) analysis enabled the detection and identification of structurally diverse *R. communis* biomolecules at different concentration levels with high mass accuracy despite the sample complexity. The application of fragmentation techniques confirmed distinct structural elements of biomarkers and provided a high-confidence structural characterisation. Currently, more than 200 metabolite and lipid species, including more than 20 *R. communis* specific biomarkers, have been identified and included in a database. Semi-quantitative analysis of identified biomolecule profiles showed distinct patterns dependent on the biotoxin purification method used and on the specific *R. communis* cultivar. The data obtained has been combined and used to build chemometric models, allowing a differentiation between crude and purified ricin materials from different extraction protocols and cultivars. Ms Scharrenbroch highlighted that these findings can be used to retrospectively categorise unknown purified ricin materials.

5.5   Based on total carbon and nitrogen isotope ratios determined by IRMS analysis, castor seeds could be distinguished in pairwise comparisons between those from a known geographical origin but unknown cultivar, and those from a known cultivar but of

unknown geographical origin (if they were purchased commercially for example). This indicates that total carbon and nitrogen isotope ratio measurements can be used to correlate potential source seeds found at a preparation site to purified ricin material at a crime scene, provided that the purification method is known. In addition, carbon and nitrogen mass concentrations can be used to estimate the degree of biotoxin purification independent of the castor seed origin. Furthermore, combining carbon and nitrogen mass concentrations and respective stable isotope ratios enables classification of unknown *R. communis* materials based on origin and biotoxin purification level for material comparison purposes.

5.6   In conclusion, Ms Scharrenbroch emphasised that the data obtained from this comprehensive analytical approach, combined with subsequent chemometric analysis, could facilitate the development of new profiling strategies to establish potential correlations between crime scenes, preparation sites, and suspects. This also suggests that molecular forensics can help link ricin preparations to specific extraction protocols and source seeds by identifying unique, characteristic patterns. Such additional forensic signatures can be implemented in profiling strategies and are of high value for forensic intelligence in terms of sample comparison.

5.7   Ms Scharrenbroch's presentation generated significant discussion among the TWG members, and a number of questions were posed, especially relating to the isotopic ratio work. As IRMS is a relatively uncommon technique at OPCW designated laboratories, the Group was interested to learn how difficult it is to implement in practical terms. Ms Scharrenbroch admitted that a lot of validation was required initially to meet international standards and ensure that the results produced are comparable with other laboratories. However, once implemented, it is very robust.

5.8   The TWG members were surprised to hear that the biological composition of castor seeds, even those from the same plant, may vary considerably. This arises due to several factors affecting the plant, including the level of light, nutrients, and water. As a result of this variation, Ms Scharrenbroch has concluded that a minimum of five seeds are required for analysis in order to produce a homogenised, representative sample. It was noted that this is important information for those collecting samples in the field.

5.9   The TWG asked about how cultivars and purification protocols were classified as either distinguishable or indistinguishable, and how the limits for these were determined. In providing an explanation, Ms Scharrenbroch also emphasised that IRMS analysis is not used to identify geographical origin, cultivars, or protocols, but is used for a material comparison and can provide an additional level of confidence in results from another analytical method.

6.   **AGENDA ITEM SIX – Discussion on end-of-mandate report**

The TWG discussed the layout and design of the end-of-mandate report. The Group agreed that the inclusion of supporting graphics would significantly enhance the readability of the report and its overall impact. In terms of content, the report should contain contributions from all subgroups to ensure a comprehensive overview of the Group's findings. The TWG also emphasised the importance of including clear recommendations for further research or implementation to guide future efforts in this area.

7. AGENDA ITEM SEVEN – Data-driven approaches for the chemical exposure assessment

7.1 Prof. Saer Samanipour, from the University of Amsterdam, the Netherlands, shared his research on investigating techniques that can be used to predict chemical signatures and toxicity in a space with many chemical unknowns.

7.2 The organic chemical space is largely unknown. The relevant space—those compounds that people may be exposed to—could be as small as 250,000 compounds, up to over two billion organic structures. In fact, it has been estimated that the total number of chemically feasible organic compounds based solely on hydrogen, carbon, nitrogen, oxygen, and phosphorus, with a molecular weight below 5000 g/mol, is approximately 10^{60}. This number of compounds is so large that it can be considered abstract, making it impossible to technically cover all the physiochemical property possibilities.

7.3 Prof. Samanipour's presentation focused on data-driven approaches to chemical exposure assessment that address the significant challenges in identifying and measuring chemicals within the vast and diverse chemical space. Current technologies like liquid chromatography and mass spectrometry are unable to fully cover this space, leading to gaps in measurable and identified chemicals. The use of advanced machine learning models and AI-based tools, such as Spec2Mol and MSNovelist, can improve structural elucidation and chemical identification.

7.4 The TWG also discussed the application of kernel density estimation and quantitative structure-activity relationship (QSAR) models for predicting chemical toxicity and mapping large chemical databases, such as CompTox, into toxicity categories. These models have shown high accuracy in toxicity prediction, reaching 80% accuracy when combined with structural fragment data. The talk further emphasises the real-world applications of these approaches, including a pesticide spiking experiment that demonstrated 70% accuracy in toxicity category assessment without prior knowledge of chemical structures.

7.5 The presentation concluded with Prof. Samanipour highlighting the existing key challenges, such as the large portion of chemical space that remains unmapped and unidentified, and the opportunities for developing new analytical technologies to improve chemical exposure assessment and environmental monitoring.

7.6 Following the presentation, the TWG members asked about the regulation of new chemicals, data that can help identify the chemical space and how it is generated, and how predicted toxicity data compare to experimentally derived data. There was a discussion about how the models and approaches presented could apply to the field of chemical weapons. Prof. Samanipour noted that the toolbox of modelling approaches presented may be useful in predicting the chemical weapons space, including associated toxicities.

8. AGENDA ITEM EIGHT – Discussion with the OPCW Declaration Assessment Team

8.1 The Head of the Declaration Assessment Team (DAT), Mr Nihad Alihodžić, along with the Lead Technical Expert, Mr Moez Hani, provided an overview of the work of the DAT covering its mandate, methodology, outcomes, and the challenges faced since it was established in 2014. The DAT continuously engaged with the relevant Syrian

authorities to resolve the identified gaps, inconsistencies, and discrepancies noted by the Secretariat in the Syrian Arab Republic's declaration regarding its chemical weapons programme upon signing and ratifying the Convention in 2013. In 2016, the DAT began looking at approaches to chemical profiling of authentic samples to aid its ongoing work by finding scientific information that could help resolve inconsistencies noted in the Syrian Arab Republic's declaration.

8.2   The DAT explained how the methodology it employs differs from those used during routine missions or during proficiency tests by the designated laboratories due to the challenges faced, the complexity of the samples, and the number of unknowns in this process. Within this context, the DAT emphasised that all relevant information—not just from the chemical samples themselves, which came from various other sources, including documents, information gathered through technical meetings, interviews, photos, or videos—was critical to identifying the best approach for profiling these authentic samples. Furthermore, the DAT underlined that profiling authentic samples requires adequate planning, which takes place prior to the collection and analysis of the samples. The DAT also explained that lessons learned from the profiling of authentic samples have been gradually implemented in the scopes of analysis which, in general, are considered critical in order to obtain data in line with the defined mandate of the mission, as well as additional activities, such as profiling. The entire picture is then used to ascertain the soundness of the declaration in question.

8.3   The DAT has collected samples from a number of declared facilities, and a few non-declared sites of relevance, in the Syrian Arab Republic. Various types of samples are taken, such as soil samples, concrete, wipes, and wood, in addition to parts of munitions, including membranes and inert burster tubes, among others. Extensive documentation is kept for all samples, ensuring a robust chain-of-custody approach that has been applied to each sample the DAT has collected.

8.4   The DAT applies chemical profiling approaches to aid in understanding collected samples and the explanations provided for the presence of certain chemicals in these samples. However, for a variety of reasons, the work remains challenging due to the following factors:

(a)   the complete environmental conditions and subsequent ageing and/or degradation of the collected samples are unknown;

(b)   multiple synthetic methods have been used for the production of the chemical warfare agents and their precursors present in the samples;

(c)   there is enormous variability in the concentrations and types of chemicals present in the samples; and

(d)   differences in data received from designated laboratories (arising from variations in the equipment and approaches used for sample analysis).

8.5   The ensuing discussion allowed the TWG to better understand the various constraints that exist in the work of the DAT. The Group had a number of questions related to the on-site sampling and subsequent laboratory analysis of DAT samples. The responses provided the TWG with a clearer picture of how authentic samples, and the conclusions that can be made, can differ greatly from work using laboratory-generated samples, which can be conducted under controlled environments and conditions.

9. **AGENDA ITEM NINE – Discussion with the OPCW Fact-Finding Mission in Syria**

9.1   Given the synergistic nature of the OPCW Fact-Finding Mission in Syria (FFM) and the Investigation and Identification Team (IIT), insofar as FFM investigations always precede those of the IIT, the two teams were asked to present sequentially and then field questions and discussion together. The two teams kept their presentations brief to allow for a substantive discussion where they could focus on providing answers to the various questions the TWG raised regarding the chemical forensics nature of their investigations.

9.2   To begin, Mr Sami Barrek, Head of the FFM, presented the work of the FFM. Mr Barrek started by introducing the team and gave an overview on the establishment, mandate, and work of the FFM since its inception, describing the field activities and the challenges it has faced during its investigations in Syria.

9.3   Mr Barrek provided an overview of the entire process of an investigation of alleged use of chemical weapons, starting with the initial allegation and assessment, followed by information gathering, triage, and classification, as well as data interpretation, through to final analysis, corroboration, and reporting. The majority of the presentation focused on the sampling and analysis of chemical samples, while noting the other types of samples and information taken and utilised, and the collective importance of all identified relevant information to the final conclusions of any investigation.

9.4   Following the presentation of the FFM, Ambassador Hernan Salinas, Chief Coordinator of the IIT, along with the Senior Legal Officer, Ms Valentina Falco, explained how the IIT identifies perpetrators of use of chemical weapons in the Syrian Arab Republic. They focused their presentation on the methodology of their work, which builds upon and is a natural continuity of the work of the FFM. Investigations of the IIT adopt a holistic approach, reviewing all evidence gathered by both the IIT and the FFM, such as documents, samples, data, reports, and statements, and systematically exploring all plausible scenarios of a proven chemical weapons incident.

9.5   Ambassador Salinas and Ms Falco also highlighted some of the challenges faced by the IIT during its investigations, especially regarding disinformation. To conclude, they explained the utility and importance of chemical forensics approaches in their investigations, such as synthetic route determination and chemical profiling. They stressed the valuable role of the designated laboratories in providing supplementary analyses that further bolster the validity of their findings.

9.6   Common to the collective work of the FFM and the IIT is the strict adherence to forensic principles. This includes maintaining the chain of custody of all samples, creating, validating, and verifying chains of evidence, data reliability, and utilising and analysing all available metadata.

9.7   After the presentations, the FFM and IIT thoroughly addressed the various questions from the Group around their investigatory processes, with a focus on chemical sampling and analysis and the application of chemical forensics approaches. The work is complex, given the limited opportunity for sample collection, both in terms of when and where samples can be collected. However, the adherence to best practices and the methodologies developed ensure a transparent, defensible approach that ultimately produces trusted results.

10. **AGENDA ITEM TEN – Discussion with the OPCW Investigation and Identification Team**

See agenda item nine.

11. **AGENDA ITEM ELEVEN – Subgroups 1 and 3 breakout sessions**

See agenda item two.

12. **AGENDA ITEM TWELVE – Subgroups 2 and 4 breakout sessions**

See agenda item two.

13. **AGENDA ITEM THIRTEEN – Forensic chemistry: Some applications of chemical profiling**

13.1 Dr Laurence Dujourdy, from l'Institut Agro Dijon, France, gave a presentation on the role of chemical profiling in illicit drug investigations. Chemical profiling is applied in the agri-food, pharmaceutical, and cosmetics sectors to ensure the quality, authenticity, safety, and traceability of products. In forensic chemistry, it is used to identify the source, purity, or potential use of a substance in a criminal activity.

13.2 Chemical profiling can be viewed as a process that starts with sampling and ends with interpretation. Data analysis and statistics play a crucial role in this process. The nature of the interpretation depends on the context and objective of the specific analysis or investigation. Dr Dujourdy stated that for forensic scientists, the ultimate goal is to interpret the evidence for the court.

13.3 Chemical profiling in the illicit drug field involves methods to define the chemical and physical properties of drug seizures. These profiles enable comparison across seizures, helping trace distribution chains for both intelligence (strategic and tactical) and evidential purposes. Illicit drug profiling enables forensic scientists to determine whether two or more drug samples originate from the same production batch by comparing their organic impurity profiles through chromatographic profile comparison. This technique is used because it is well established, fast, inexpensive, and easy to set up, especially when compared to other methods.

13.4 Dr Dujourdy explained how this comparison is performed. The signal obtained from the analysis is considered a vector with as many components as there are chromatographic peaks, and all the results are arranged in tabular form. These vectors are compared by calculating a metric, which can be a distance or a similarity. The distances or similarities between pairs of samples is represented by a matrix. Two distance distributions are then constructed. One corresponds to samples assumed to be linked (samples from the same large seizure or samples known to be from the same production batch) and the other corresponds to unlinked samples (from seizures that are distant in time or known not to be related). In general, these two distributions overlap, and the aim is to identify a model with as little overlap as possible in order to reduce the false positive rate. Once the model has been validated, it can be used routinely to provide information in the form of a crime analysis chart, for example. Dr Dujourdy provided two case studies where this methodology was used in agri-food analysis.

13.5 In closing, Dr Dujourdy introduced a current research project which aims to leverage symbolic and statistical AI to extract information from a large dataset of drug analysis data that has been developed over many years.

13.6 Following the presentation, Dr Dujourdy was asked how low-abundance markers can be distinguished in profiles with high-abundance—and usually less useful—markers. She informed the Group that the data undergoes a pre-treatment process to normalise it and correct the effects of high concentrations of particular markers.

13.7 Regarding natural variability in the drug samples, she stated that it is important to analyse a large number of samples, and this means that natural variability can be modelled. However, due to the low numbers of samples, it is impossible to have reliable chemical profiling methods for emerging drugs. Dr Dujourdy added that when time permits, staff at l'Institut Agro Dijon synthesise drugs using recipes retrieved from the internet to bolster available data.

13.8 The TWG members showed particular interest in data sharing. Dr Dujourdy explained that following a surge of illicit amphetamines across Europe in the early 2000s, a Europe-wide database was established. Laboratories adopted harmonised methods to compare samples from different laboratories, and the data were shared within a centralised system. Strict protocols govern the management and curation of this database. This approach is so effective because all laboratories use identical instruments and methods, ensuring that data can be reliably compared. New instruments must undergo revalidation, which is both laborious and time-consuming. For heroin and cocaine, there is no Europe-wide shared database; instead, data are managed at the national or regional level. Dr Dujourdy further noted that in France, all forensic laboratory data are entered into a single, national database. This is unusual, as laboratories typically maintain their own individual databases.

14. AGENDA ITEM FOURTEEN – Recaps from subgroup leads

See agenda item two.

15. AGENDA ITEM FIFTEEN – Closing remarks and any other business

Dr Bossée briefly summarised the key points discussed during the meeting and noted that the fourth meeting of the TWG is scheduled from 22 to 24 January 2025. No additional points were raised.

16. AGENDA ITEM SIXTEEN – Closure of the meeting

The Chairperson ended the meeting at 16:35 (CET) on 27 September 2024.

ACKNOWLEDGEMENTS

Annex: List of Participants at the Third Meeting of the Scientific Advisory Board's Temporary Working Group on Chemical Forensics

Annex

LIST OF PARTICIPANTS AT THE THIRD MEETING OF
THE SCIENTIFIC ADVISORY BOARD'S TEMPORARY WORKING GROUP
ON CHEMICAL FORENSICS

	Participant	**Institution**
1.	Prof. Arian van Asten	University of Amsterdam, Netherlands
2.	Dr Crister Åstot[*]	Swedish Defence Research Agency (FOI), Sweden
3.	Capt. Elma Biscotti[*]	Scientific and Technical Research Institute for Defense (retired), Argentina
4.	Dr Anne Bossée[*] (Chairperson of the TWG)	DGA CBRN Defence, France
5.	Dr Grégoire Delaporte	DGA CBRN Defence, France
6.	Ms Anne-Marie Fortin	United Nations Office on Drugs and Crime, International
7.	Dr Hanna Hakulinen	Finnish Institute for Verification of the Chemical Weapons Convention (VERIFIN), Finland
8.	Ms Ang Lee Hwi	DSO National Laboratories, Singapore
9.	Prof. Imee Su Martinez[*]	University of the Philippines Diliman, Philippines
10.	Dr Simon Ovenden (Vice-Chairperson of the TWG)	Defence Science and Technology Group, Australia
11.	Mr Günter Povoden[*]	CBRN Defence Centre, Austrian Armed Forces, Austria
12.	Prof. Ines Primožič[*]	University of Zagreb, Croatia
13.	Dr Sarah Stubbs	Defence Science and Technology Laboratory, United Kingdom of Great Britain and Northern Ireland
14.	Dr Hongmei Wang	State Key Laboratory of NBC Protection for Civilian, China
15.	Dr Audrey Williams	Lawrence Livermore National Laboratory, United States of America
16.	**Invited Speakers**	**Institution**
17.	Dr Laurence Dujourdy	L'Institut Agro Dijon, France
18.	Dr Karin Höjer Holmgren	Swedish Defence Research Agency (FOI), Sweden
19.	Dr Saer Samanipour	University of Amsterdam, Netherlands
20.	Ms Lisa Scharrenbroch	Federal Criminal Police Office, Germany
21.	**Technical Secretariat Staff**	**Division**
22.	Mr Nihad Alihodžić	Head, DAT
23.	Ms Valentina Falco	IIT
24.	Mr Moez Hani	DAT
25.	Dr Peter Hotchkiss (Secretary to the SAB)	Office of Strategy and Policy
26.	Ambassador Hernan Salinas	Chief Coordinator, IIT

[*]   Member of the SAB.

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