

29 November 2024

9:30-13:00

MINUTES - Agreed on 17 December 2024

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Chaudhry Mohammad, Eva Bay Wedbye, Emilio Benfenati
- EFSA:
MESE Unit: Alexis Nathanail (Chair)

I. Welcome and apologies for absence

The Chair welcomed the participants. No Apologies were received.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. Final QSAR results by VEGA and Danish EPA QSAR models

The final QSAR results retrieved by VEGA and Danish EPA models for all endpoints, including acute toxicity, genotoxicity, carcinogenicity, reproductive toxicity, systemic toxicity (hepatotoxicity, nephrotoxicity and cardiac toxicity), as well as endocrine activity have been completed and were submitted to EFSA by the experts of the Botanicals Working Group (WG).

V. Consensus outcomes in the database

Alongside the results of the individual outcomes for all the endpoints described above, also the consensus outcomes for all substances were reached, based on the consensus strategy previously developed by the WG, and are ready for inclusion in the Compendium of Botanicals database. With these QSAR outcomes the final stage of development of the database will soon commence prior to its launch in Q1 2025.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

14 October 2024

9:30-13:00

MINUTES - Agreed on 30 October 2024

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Chaudhry Mohammad, Eva Bay Wedbye, Emilio Benfenati
- EFSA:
MESE Unit: Alexis Nathanail (Chair)

I. Welcome and apologies for absence

The Chair welcomed the participants. No Apologies were received.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. Update on the Compendium of Botanicals database development

An update was provided to the experts of the Working Group (WG) on the development of the expanded Compendium of Botanicals database that will include additional information on plants and toxicological information on substances of potential concern. The new layout of the database was displayed and comments by the experts were received that will be addressed in the on-going development work of the database.

V. QSAR results by VEGA and Danish EPA QSAR models

The individual QSAR predictions for the remaining chemicals will become available at the end of October. Following completion of the QSAR predictions the experts will reach the

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



consensus outcome for those endpoints with conflicting predictions based on the strategy developed by the WG on Botanicals. The consensus outcomes for all endpoints will be finalised by the end of November and be ready for integration into the database.

VI. Presentation of QSAR consensus outcomes in database

The WG discussed and agreed on the type of information and layout of the QSAR outcomes to be presented in the database. The template to host this data will be soon developed prior to making the new database publicly available.

VII. Progress update on scientific publications

The work on the publication will resume after all results are ready and the consensus outcomes of the QSAR predictions have been reached.

VIII. AOB and 2024 meetings

Next meeting 29th of November 2024 (web meeting).

3 July 2024

9:30-16:30

MINUTES - Agreed on 22 July 2024

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Chaudhry Mohammad, Eva Bay Wedbye, Emilio Benfenati
- EFSA:
MESE Unit: Alexis Nathanail (Chair)
Know Unit: Bernard Bottex

I. Welcome and apologies for absence

The Chair welcomed the participants. No Apologies were received.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. Update on the Compendium of Botanicals database development

An update was provided to the Working Group (WG) experts regarding the development of the expanded Compendium of Botanicals database that will include additional information on plants and toxicological information on substances of potential concern.

V. Update from the EU activities on Food Supplements and request for QSAR data

Bernard informed the experts about an on-going initiative of the Community of Knowledge on Food Supplements (coordinated by Anses), aiming at identifying emerging risks related to food supplements. Partners involved in this activity are interested in the use of the

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



Compendium data, with a special focus on the substances with predicted toxicity. Potential ways to support this activity via the outcomes generated by the Botanicals WG were proposed and discussed.

VI. Quality check of chemical info of substances, QSAR analysis of remaining substances and consensus outcomes

Agreement was reached on how to finalise the quality control on chemical identity information of the substances of potential concern that are included in the Compendium of Botanicals. The experts will seek and verify this information for substances with data gaps from reliable scientific sources and update the database accordingly.

VII. Progress update on scientific publications

The current state of the scientific publication was discussed; an overview of the text was presented, as well as the general structure of the draft paper. Comments on the text were provided and addressed and the draft will soon be finalised.

VIII. AOB and 2024 meetings

Next meeting pending confirmation.

CUMULATIVE MEETING MINUTES

January 2023 – February 2024

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Robert Anton, Ulla Beckman-Sundh, Carlo Bicchi, Qasim Mohammad Chaudhry, Massimo Collino, Wirginia Kukula-Koch, Kirsten Pilegaard, Mauro Serafini and Luigi Milella
- EFSA:
MESE Unit: Alexis Nathanail
NIF/FEEDCO Unit: Eirini Kouloura

I. Adoption of agenda

Due to the specific and similar format of the meetings (one-to-one meetings between each expert and EFSA staff to review relevant information extracted for substances assigned), no formal agenda was drafted.

II. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group (WG) members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

III. Screening of scientific articles – Toxicity characterisation

The experts of the WG on Botanicals participated in bilateral meetings to validate information retrieved in the literature for the characterisation of the toxicity of substances of potential concern present in the Compendium of Botanicals. Toxicity information was collected for 1,518 naturally occurring substances in plants and approximately 60,000 articles were screened to extract information relevant to the toxicity of the substances.

Between January 2023 and March 2024, 39 bilateral meetings of 3 h were held between an expert and an EFSA Officer to validate the information extracted relevant to the toxicity of the substances. Minutes for single meetings have been replaced by one single document summarising all the meetings held during this period.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



In Annex I below further information on the meetings dates and participation of experts is presented.

Annex I

Meetings- Participants	Dates
WG Botanicals - Substances review - Ulla Beckman	24/03/2023
WG Botanicals - Substances review - Qasim Chaudhry	27/04/2023
WG Botanicals - Substances review - Mauro Serafini	16/05/2023
WG Botanicals - Substances review - Robert Anton	22/05/2023
WG Botanicals - Substances review - Massimo Collino	24/05/2023
WG Botanicals - Substances review - Carlo Bicchi	24/05/2023
WG Botanicals - Substances review - Kirsten Pilegaard	30/05/2023
WG Botanicals - Substances review - Wirginia Kukula	31/05/2023
WG Botanicals - Substances review - Luigi Milella	13/06/2023
WG Botanicals - Substances review - Kirsten Pilegaard	06/07/2023
WG Botanicals - Substances review - Mauro Serafini	11/07/2023
WG Botanicals - Substances review - Luigi Milella	13/07/2023
WG Botanicals - Substances review - Carlo Bicchi	14/07/2023
WG Botanicals - Substances review - Robert Anton	17/07/2023
WG Botanicals - Substances review - Massimo Collino	19/07/2023
WG Botanicals - Substances review - Qasim Chaudhry	25/07/2023
WG Botanicals - Substances review - Ulla Beckman	26/07/2023
WG Botanicals - Substances review - Wirginia Kukula	31/07/2023
WG Botanicals - Substances review - Robert Anton	23/10/2023
WG Botanicals - Substances review - Kirsten Pilegaard	03/11/2023
WG Botanicals - Substances review - Ulla Beckman	06/11/2023
WG Botanicals - Substances review - Carlo Bicchi	07/11/2023
WG Botanicals - Substances review - Qasim Chaudhry	09/11/2023
WG Botanicals - Substances review - Luigi Milella	13/11/2023
WG Botanicals - Substances review - Wirginia Kukula	14/11/2023
WG Botanicals - Substances review - Mauro Serafini	20/11/2023
WG Botanicals - Substances review - Massimo Collino	24/11/2023
WG Botanicals - Substances review - Carlo Bicchi	15/12/2023
WG Botanicals - Substances review - Luigi Milella	18/12/2023
WG Botanicals - Substances review - Kirsten Pilegaard	19/12/2023
WG Botanicals - Substances review - Ulla Beckman	20/12/2023
WG Botanicals - Substances review - Carlo Bicchi	21/12/2023
WG Botanicals - Substances review - Massimo Collino	09/01/2024

CUMULATIVE MEETING MINUTES January 2023 – February 2024
Botanicals Working Group Meetings on Toxicity Characterisation



WG Botanicals - Substances review - Wirginia Kukula	11/01/2024
WG Botanicals - Substances review - Ulla Beckman	16/01/2024
WG Botanicals - Substances review - Qasim Chaudhry	17/01/2024
WG Botanicals - Substances review - Ulla Beckman	25/01/2024
WG Botanicals - Substances review - Carlo Bicchi	14/02/2024
WG Botanicals - Substances review - Robert Anton	29/02/2024

Location: EFSA - Parma (Meeting Room 00/M05)/Webconference

Attendees:

- Working Group Members:

Carlo Bicchi, Ulla Beckman, Qasim Chaudhry, Massimo Collino, Wirginia Kukula, Kirsten Pilegaard, Mauro Serafini, Luigi Milella (online), Eva Bay Wedbye, Emilio Benfenati (2nd day online)

- Hearing Experts:

Krystof Dibusz, Klara Nicova

- EFSA:

MESE Unit: Alexis Nathanail (Chair), Georgia Bompola

FEEDCO Unit: Eirini Kouloura

KNOW Unit: Bernard Bottex, Milen Georgiev

iDATA Unit: Luca Belmonte, Edoardo Carnesecchi

1. Welcome and apologies for absence

The Chair welcomed the participants.
Apologies were received from Robert Anton.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group (WG) members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

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4. Tour de table

The participants in the meeting introduced themselves, their expertise and other relevant activities.

5. Compendium of Botanicals: Overview of the activity and current status

An overview of the activities within EFSA Compendium of Botanicals since its inception was given. In the Plant Screening activity, which has been finalised in January 2023, approximately 2700 plant were evaluated for identification of potential hazards for humans by systematic literature search. Information on compounds of concern and toxicological data attributed to these plant species was extracted. Regarding the Toxicity Characterisation of Substances activity, a systematic literature search was performed for 1700 substances, which were identified in the plant screening activity as substances of potential concern. Among them, 625 substances were identified with literature toxicity data that required screening by the experts. The last 75 substances are currently being screened by the experts.

The experts noted that the taxonomy of the plants is constantly changing, and it was agreed that the database will be published with the taxonomy that was valid during its development, noting the date and adding a disclaimer that the taxonomy is continuously evolving. It remains to be decided within EFSA how often the content of the Compendium is going to be reviewed and updated as new data become available.

6. Toxicity characterisation of natural substances (ChemCombo)

The experiences of experts during the screening of the substances using the ChemCombo platform was evaluated as positive. A few minor technical issues related to the literature screening were raised and discussed.

7. *In silico* toxicity assessment of botanical substances

A presentation on the way *in silico* methods can fit in the toxicity characterisation strategy for regulatory risk assessment was provided, highlighting that *in silico* testing can be exploited as supporting evidence. Subsequently, the methodologies that were used for the quality check of the predicted toxicity of all substances in the Compendium using VEGA, Danish QSAR Database and T.E.S.T. models were presented. CAS/SMILES for all substances were manually checked and the identity of substances without CAS or SMILE was confirmed through searches in Scifinder, ChemIdPlus and Pubmed databases.

8. VEGA QSAR models and results

Features of the VEGA QSAR models were demonstrated. The Applicability Domain Index (ADI) attributed to each prediction to assess the reliability gives greater confidence in the



predictions made by the tool. A summary of the QSAR results for each different endpoint after testing the total amount of the substances was then provided.

9. Danish QSAR database and results

The results for the genotoxicity endpoints were presented after a brief introduction of the models used. The Danish QSAR includes data from REACH pre-registered and registered substances, as well as information about EU harmonised CLP classifications.

10. Ecomole - contractor's point of view

An overview of the PlantCombo database was provided, stressing out the problem of mismatches of identification of plants between the ones in Combo and the one in EFSA MTX Catalogue, which were sorted out manually, leading to the update of the MTX catalogue.

A presentation of the platform for the screening of the substances (ChemCombo) followed, as the more user-friendly evolution of the platform that was used for the plant screening (PlantCombo). The contractors noted that for substances with >500 articles retrieved an additional targeted screening was performed to retrieve articles on genotoxicity, reproductive toxicity, systemic toxicity and carcinogenicity. Regarding the current status of the platform, targeted screening is almost completed while next steps involve data validation and their submission to EFSA together with the final report.

The new features and possibilities of Ecomole platforms were described, pointing out that despite the increased exploitation of AI, it is crucial that data verification remains on expert judgement.

11. Collection, assessment and visualisation of botanicals data

The iData Unit shared updates on the development of the data model to facilitate the upcoming integration of new data for the substances of potential concern. Following the final submission of the new data, tests still need to be conducted before launching the updated "Compendium of Botanicals" database and its companion dashboard.

12. Community of knowledge for the identification of emerging risks related to botanical food supplements

Due to the emerging risks deriving from plant-based food supplements a community of knowledge with the participation of Member States and other stakeholders will be proposed in 2024, to address issues related to the safety of botanicals. In that sense the EFSA Compendium of Botanicals will be used as the basis to facilitate identification of plant species containing compounds of concern or exhibit toxicological effects to humans, plant-based substances of concern with predicted toxicity, and assist the hazard identification for the safety assessment of plants that are used in/as food supplements.



13. Closing remarks

The activities of the WG were summed up and the future steps were described, focusing on the date of the submission of the data by Ecomole and the publication of the updated Compendium of Botanicals database without the QSAR predictions (expected within 2024). The QSAR sub-group will continue working on the prediction of the toxicity of the substances. Following the publication of the Compendium of Botanicals database, a survey may be conducted to acquire an understanding of its usefulness.

2 October 2023

9:30-17:00

MINUTES - Agreed on 16 October 2023

Location: Teleconference

Attendees:

- Working Group Members:
Chaudhry Mohammad, Eva Bay Wedeby, Emilio Benfenati
- EFSA:
MESE Unit: Alexis Nathanail (Chair), Fotios Spyropoulos

I. Welcome and apologies for absence

The Chair welcomed the participants. No Apologies were received.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. QSAR analysis of remaining substances and quality check of chemical info of new substances

A quality control was performed on the data from the new and final batch of substances to be included in the Compendium of Botanicals. From the new substances, 340 had CAS numbers and SMILES, 76 did not have a CAS number, 57 had a CAS number but not SMILES and 19 had no CAS number nor SMILES. The experts will seek chemical identity information for the substances with data gaps from other sources and update the database accordingly. All chemical identification information will be quality checked by the experts.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



V. QSAR template mandatory fields for database

The information to be displayed in the database regarding QSAR data was discussed. It was suggested that SMILES, CAS number, 2D structure and model reliability scores should be also included, together with the QSAR results. The VEGA QSAR system can provide documentation for predictions that could be added in the database for user reference. Overall, the outline of the QSAR templates in the database will be developed in a simple and user-friendly format.

VI. Demonstration of the VERA read-across tool

The previous and new versions of the Virtual Extensive Read-Across (VERA) tool were presented, together with a case study on its use to conduct read-across for the carcinogenicity hazard class. It was suggested that read-across could be deployed on chemicals that have no information at all, or unequivocal or negative results from QSAR predictions.

VII. Progress update on scientific publications

The current state of the publication was discussed. An overview of the text was presented, as well as the general structure of the draft paper. Comments on the text were provided and addressed, and the draft will soon be finalised.

VIII. AOB and 2023 meetings

Next meeting pending confirmation.

4 July 2023

9:30-12:30/14:00-16:30

MINUTES - Agreed on 11 July 2023

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Chaudhry Mohammad, Eva Bay Wedbye, Emilio Benfenati
- EFSA:
MESE Unit: Alexis Nathanail (Chair), Jean Lou Dorne¹, Fotios Spyropoulos
iDATA Unit: Edoardo Carnesecchi², Luca Belmonte²

I. Welcome and apologies for absence

The Chair welcomed the participants.

II. Adoption of agenda

The agenda was adopted without changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence³ and the Decision of the Executive Director on Competing Interest Management⁴, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. QSAR templates (OHT and database reporting format)

The discussion was initiated with the EFSA-ECHA project on structuring and reporting QSAR data into IUCLID, within the scope of OECD Harmonized Templates (OHTs). The project objectives were presented, as well as the methodology and the results of the project. Comments were made on the IUCLID platform regarding QSAR predictions' assessment and the QSAR Modeling Reporting Format (QMRF). A discussion followed on the whether QSAR results should be presented as a single outcome derived from the consensus of different models for each hazard class or the individual values derived from each model. Finally, the experts were asked to identify which QSAR parameters and information are considered essential to be included in the presentation of QSAR data in the Compendium of Botanicals database.

¹ Attended agenda item VIII

² Attended agenda item IV

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

⁴ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



V. Botanicals WG work updates

An update on the broader activities of the Botanicals WG was provided to the experts, including the finalisation of work from the contractor and delivery of botanical plant species data in a compatible format for EFSA's data infrastructure. The progress of the toxicity characterisation work of substances using literature data was also presented.

VI. QSAR analysis of remaining substances

The predictions for the remaining substances followed the same process as the previous batch. Some substances did not have reported SMILES codes. For those substances, QSAR predictions are pending until accurate SMILES are found. Quality check of SMILES for the new substance will be conducted.

VII. Decision on the use of read-across

It was suggested that read-across could be deployed when no literature or QSAR results have been obtained for substances of potential concern. In the case of no data availability, structurally similar compounds can be used to predict toxicity via "automated read-across" using computational models. The data gathered from literature can provide a repository of toxicity information that could be utilised for the purposes of read-across. It was suggested that also for substances without SMILES, read-across could be an alternative source of information.

VIII. Progress update on scientific publications

The progress of the publication for EFSA's QSAR for Botanicals work was presented and discussed. A complete draft of the manuscript is expected to be ready by the end of July.

IX. AOB and 2023 meetings

Next WG meeting will take place on 6 September 2023 (online meeting via TEAMS).



SCIENTIFIC COMMITTEE

Botanicals Working Group Meeting on Toxicity Characterisation



4 April 2023

9:30-16:00

MINUTES - Agreed on 19th of April 2023

Location: Web Conference (TEAMS)

Attendees:

Working Group Members:

Chaudhry Mohammad, Bay Wedbye Eva, Emilio Benfenati

EFSA:

MESE Unit: Nathanail Alexis (Chair), Spyropoulos Fotis, Jean Lou C.M. Dorne¹

KNOW Unit: Bernard Bottex¹

I. Welcome and apologies for absence

The Chair welcomed the participants.

II. Adoption of agenda

The agenda was adopted without any changes.

III. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

IV. QSAR predictions for remaining substances

A general discussion was made on the progress of the Working Group (WG) for the toxicological characterisation of substances of potential concern by the experts. The last batch of substances to be analysed with the QSAR models has been made available by the contractor and a plan was agreed on how to proceed with the computational processing.

V. Finalisation of genotoxicity outcomes

The remaining results of the QSAR models for genotoxicity outcomes were discussed and finalised. The chromosomal aberration criteria were further refined in order to apply a similar consensus strategy of QSAR outputs to those of the other genotoxicity endpoints.

¹ Attended in agenda items IX and X

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



VI. Finalisation of acute toxicity and carcinogenicity outcomes

It was decided that for acute toxicity outcomes the LD50 values will be reported together with the source of the data. Carcinogenicity outcomes were already completed from the previous WG meeting.

VII. Finalisation of reproductive toxicity outcomes

Compared to other endpoints reproductive toxicity is more complex, due to the wide range of effects. It was agreed that the reproductive toxicity outcomes will be based on the PG and DQD models in addition to the rodent dominant lethal mutation test results.

VIII. Decision on systemic endpoints (hepatotoxicity, nephrotoxicity and cardiac toxicity), endocrine activity and read-across

Systemic endpoint predictions are based on the presence of moieties/groups of concern in molecules. The systemic QSAR predictions will be presented as toxicological alerts based on the results of the available models for each endpoint. Alerts for endocrine activity will also be presented in the database. Read-across will be deployed when equivocal data are presented or when there are no available literature or QSAR data.

IX. Progress update on scientific publications

A poster for the 2023 EUROTOX conference (10-13/9/2023, Ljubljana, Slovenia) describing the Botanicals database will be presented. Moreover, a scientific publication concerning the QSAR work and results is currently under preparation.

X. AOB and 2023 meetings

The next WG meeting will be held on 04/07/2023 (Teleconference).

07 February 2023

09:30-17:00

MINUTES - Agreed on 16 February 2023

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Emilio Benfenati, Eva Bay Wedebye, Qasim Chaudhry¹
- EFSA:
MESE Unit: Alexis Nathanail (Chair), Fotis Spyropoulos

I. Welcome and apologies for absence

The Chair welcomed the participants. The agenda was adopted without changes.

II. Declarations of Interest of Working Group members

In accordance with EFSA's Policy on Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

III. Toxicity characterisation plans 2023

By the end of December 2022, the plant characterisation work was completed. Based on available literature, the toxicity characterisation of substances identified as of potential concern will be performed. This activity of the project is foreseen to start this March and the working group (WG) experts have already been informed on the workload, plans and processes to be followed. IUCLID implementation for the database was also discussed in the WG, together with suitable templates for presenting QSAR data.

IV. Genotoxicity outcomes

The genotoxicity outcomes for Ames, *in vitro/in vivo* micronucleus test, chromosomal aberration and comet assays were provided. The inclusion of both categories for positive and potentially positive data was discussed. Micronucleus *in vitro* calls were based on VEGA model predictions, whereas *in vivo* micronucleus calls are based on both VEGA 2-model-battery and DQD 3-model battery. Chromosomal aberration calls are based on 7 different models and *in vivo* comet assay calls are based on 3 DQD models. A summary of all calls for all genotoxicity was presented.

¹ Participated in I-III and V-VIII

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf



V. Acute toxicity, carcinogenicity and reproductive toxicity outcomes

Acute toxicity results were generated based on the CLP Regulation classification scheme according to LD50 values. It was agreed that the most conservative LD50 values should be reported, when more than one LD50 predictions are available. Carcinogenicity QSAR predictions from the VEGA and DQD models and their integration were presented for positive predictions (positive experimental, positive and potentially positive), as well as negative and negative experimental outcomes. For reproductive toxicity, the outcomes of CAESAR and PG models were presented. T.E.S.T. data can provide additional input on how the final results can be refined. A more comprehensive strategy combining all available data will be further developed for reproductive toxicity.

VI. Progress update on scientific publications

A paper outline focusing on the technical elements of the QSAR methodology used for the botanical substances' toxicity characterisation was discussed. The scope and contents of the paper were agreed together with a plan on how to proceed.

VII. AOB and 2023 meetings

The next meeting will be held on 04/04/2023 (Teleconference).

Location: Web Conference (TEAMS)

Attendees:

- Working Group Members:
Bicchi Carlo, Beckman Sundh Ulla, Chaudhry Mohammad, Collino Massimo, Pilegaard Kirsten, Robert Anton, Kukula-Koch Wirginia, Milella Luigi, Serafini Mauro (apologies)
- EFSA:
MESE Unit: Nathanail Alexis (Chair), Spyropoulos Fotis
NIF Unit: Kouloura Eirini
KNOW Unit: Bottex Bernard
- Contractor:
EcoMole: Nicova Klara

I. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were received from Serafini Mauro.

II. Adoption of agenda

The agenda was adopted without changes.

III. Tour de table

Everyone in the Working Group (WG) introduced themselves.

IV. Botanicals WG state of play

An overview of the completed and on-going work was presented to the WG. The plant characterisation work was finalised in January 2023 and the QSAR processing will be ready by summer 2023. The future direction of the WG is to complete the QSAR processing, the characterisation of the toxicity of identified substances of potential concern and the construction of the Botanicals database.

V. ChemCombo refresh training

The ChemCombo training started with instructions for the experts on how to access the database. The template containing the studies and relevant information on substances was presented, together with the filtering function to search for particular information in ChemCombo. Furthermore, a case study on how to operate the system was demonstrated by the trainer.



VI. Proposed methodology for toxicity characterisation of botanical substances

The proposed methodology for the toxicity characterisation of botanical substances with literature data was discussed. Inclusion and exclusion criteria of literature studies are included in the presentation which is available to the experts. An OpenFoodTox (OFT) notification in the ChemCombo entries signifies the existence of an EFSA opinion for a substance. In case of compounds that appear in multiple opinions, all EFSA opinions must be screened. The main course of action is examination of EFSA opinions, when available, and assessment of relevant articles post EFSA opinion. The top 50 relevant articles as identified in ChemCombo will need to be manually assessed for all substances by the experts.

VII. Q&A and AOB

Regarding the future of the WG and after finalisation of this project, there are possible new regulatory activities at EFSA for botanical plants that can utilise the expertise of the Botanicals WG.



Methodology & Scientific Support Unit

SCIENTIFIC COMMITTEE

CUMULATIVE MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

(Agreed on 06 January 2023)

Participants

■ Working Group Members:

Robert Anton, Ulla Beckman-Sundh, Carlo Bicchi, Qasim Mohammad Chaudhry, Massimo Collino, Wirginia Kukula-Koch, Kirsten Pilegaard, Mauro Serafini and Luigi Milella

■ EFSA:

MESE Unit: Justyna Slodek-Wahlstrom, Klara Nicova, Eirini Kouloura

1. Adoption of agenda

Due to the specific and similar format of the meetings (one-to-one meetings between each expert and EFSA staff to review relevant information extracted for plants assigned), no formal agenda was drafted.

2. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process.

3. Compendium of Botanicals database development

During the period from January to December 2022, the WG of the Compendium of Botanicals reviewed a total number of 355 plants listed in the Compendium of Botanicals. The activity involves the screening of literature data retrieved for each plant and the validation of the information extracted in the Compendium of substances of possible concern and toxicity data associated with those plants. The extracted information is awaiting to be transferred to the EFSA database.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

To achieve the above objective, 49 bilateral 3h meetings between expert and EFSA staff were held in this period. In the Annex I below further information on the meetings dates and participation of experts is available.

Minutes for single meetings have been replaced by one single document summarising all the meetings held between January to December 2022.

Annex I

Meetings- Participants	Dates
WG Botanicals - Plants review- Carlo Bicchi	17/03/2022 am
	18/03/2022 am
WG Botanicals - Plants review- Massimo Collino	21/03/2022 am
	22/03/2022 am
WG Botanicals - Plants review- Massimo Collino	31/03/2022 am
	01/04/2022 am
WG Botanicals - Plants review - Luigi Milella	20/04/2022 am
	21/04/2022 am
WG Botanicals - Plants review - Carlo Bicchi	27/04/2022 am
	28/04/2022 am
WG Botanicals - Plants review- Robert Anton	04/05/2022 am
	06/05/2022 am
WG Botanicals - Plants review - Wirginia Kukula-Koch	17/05/2022 am
	18/05/2022 am
WG Botanicals - Plants review - Kirsten Pilegaard	31/05/2022 am
	01/06/2022 am
WG Botanicals - Plants review - Robert Anton	25/05/2022 am
	30/05/2022 am
WG Botanicals - Plants review - Mauro Serafini	23/05/2022 pm
	24/05/2022 pm
WG Botanicals - Plants review - Mauro Serafini	08/06/2022 am
	08/06/2022 pm
WG Botanicals - Plants review - Luigi Milella	15/06/2022 am
	16/06/2022 am
WG Botanicals - Plants review - Carlo Bicchi	20/06/2022 am
	21/06/2022 am
WG Botanicals - Plants review - Massimo	27/06/2022 am
	28/06/2022 am
	30/06/2022 am
WG Botanicals - Plants review - Carlo Bicchi	20/07/2022 am
	20/07/2022 pm
	21/07/2022 am

WG WG Botanicals - Plants meeting - Robert Anton	05/09/2022 am
	06/09/2022 am
WG WG Botanicals - Plants meeting - Robert Anton	26/09/2022 am
WG WG Botanicals - Plants meeting - Robert Anton	10/10/2022 am
WG Botanicals - Plants review - Kirsten Pilegaard	18/10/2022 am
	19/10/2022 am
WG Botanicals - Plants review - Luigi Milella	13/10/2022 pm
	17/10/2022 pm
WG Botanicals - Plants review - Kirsten Pilegaard	25/10/2022 am
WG Botanicals - Plants review - Virginia Kukula	14/11/2022 am
	15/11/2022 am
WG Botanicals - Plants review - Ulla Beckman	16/11/2022 am
	18/11/2022 am
WG Botanicals - Plants review - Robert Anton	17/11/2022 pm
WG Botanicals - Plants review - Robert Anton	13/12/2022 am
WG Botanicals Plants review - Virginia Kukula	02/12/2022 am
WG Botanicals Plants review - Ulla Beckman	09/12/2022 am

4. Next meeting

The activity of the validation of the relevant information extracted for plant species in the Compendium of Botanicals is completed in December 2022. In 2023, the experts of the WG Compendium of Botanicals will participate in bilateral meetings to validate information retrieved in the literature for the characterisation of the toxicity of the substances of potential concern present in the Compendium of Botanicals.



Methodology & Scientific Support Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 25 November 2022, online

(Agreed on 14 December 2022)

Participants

■ Working Group Members:

Emilio Benfenati, Qasim Chaudhry

■ EFSA:

MESE Unit: Alexis Nathanail (Chair), Fotis Spyropoulos

NIF Unit: Eirini Kouloura¹

iDATA Unit: Edoardo Carnesecchi², Mayla Metitiero²

1. Welcome and apologies for absence

The Chair welcomed the participants. Apologies were sent by Eva Bay Wedebye.

2. Adoption of agenda

The agenda was adopted without any changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence³ and the Decision of the Executive Director on Competing Interest Management⁴, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues

¹ Attended topics 1-5

² Attended topic 4

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

⁴ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. General matters

The future development of OpenFoodTox was described, as well as the unification of toxicodynamics and toxicokinetics data within the platform. Furthermore, the Working Group (WG) discussed the opportunities presented by the decision to create the Botanicals database utilising the International Uniform Chemical Information Database (IUCLID) system.

For the Botanicals work, there was an update on the plant characterisation part of the project, which has almost been finalised (expected completion in 01/2023). An additional 200 substances are expected to be included in the list of 1100 substances already identified as of potential toxicological concern. Those compounds will also be analysed by the VEGA and Danish Quantitative Structure Activity Relationship (QSAR) models. Literature information on the shortlisted substances is currently being gathered as foreseen in the procurement project.

5. Botanicals QSAR data – OECD templates

IUCLID was presented as a single access source of information on chemicals, because it provides the capacity for data extraction with harmonised data formats. The first objective discussed was the transfer of the compendium of botanicals from existing software tools to IUCLID, in collaboration with the European Chemicals Agency (ECHA). The second objective is the incorporation of a harmonised template into IUCLID to present and integrate data from QSAR models in computer readable form.

6. QSAR outcomes

For the acute toxicity, the LD50 data were presented with 462 Vega predictions being below the cut-off value of 2000 mg/kg; 80 LD50 values were extracted from experimental data. For carcinogenicity, the QSAR results were the following: positive (30), equivocal (117) and negative (54). The equivocal results will be revised after adjusting certain parameters in the consensus protocol. Endpoints for developmental toxicity are available from the Danish QSAR and VEGA models that have been identified as complimentary endpoints/predictions; work on the toxicity outcomes of this hazard class are ongoing.

7. Any other business and 2023 meetings

Next WG meeting 7th of February 2023 – TEAMS meeting (9.30-17.00)



SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

**Held on 1 September 2022, online
(Agreed on 20 September 2022)**

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye

- EFSA:

MESE Unit: Alexis Nathanail (Chair)

KNOW Unit: Bernard Bottex

1. Welcome and apologies for absence

The Chair welcomed the participants. No apologies for absence were received.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Update from Genotoxicity WG discussion on use of QSAR data

Qasim provided an update to the Working Group (WG) regarding discussions held on the use of QSAR genotoxicity data with the experts of the WG on Genotoxicity. Overall, there was agreement from the Genotoxicity WG experts with the proposed approach used to deal with genotoxicity QSAR predictions.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Additional technical advice was provided in specific questions on the assessment of genotoxicity predictions generated by different models.

5. Toxicity predictions - Methodological considerations

The WG finalised the consensus approaches for the QSAR data for the hazard classes of acute toxicity, genotoxicity, carcinogenicity and reproductive toxicity. The next step is to apply the consensus strategy on the generated QSAR data, with VEGA and Danish QSAR systems, for all substances included in the database that are within the applicability domain of the models.

6. Next meeting

- 23 November 2022 (tentative), 9.30-12.30, 14.00-17.00 – TEAMS meeting



Methodology & Scientific Support Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 7 June 2022, online

(Agreed on 23 June 2022)

Participants

■ Working Group Members:

Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye

■ EFSA:

MESE Unit: Alexis Nathanail (Chair), Klara Nicova

KNOW Unit: Bernard Bottex, Melina Steinbach

■ External contractor:

ECOMOLE: Krystof Dibusz¹

1. Welcome and apologies for absence

The Chair welcomed the participants. No apologies for absence were received.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the

¹ Participated in agenda point 4 and 5.

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process.

Certain interests were declared orally by one member before the beginning of the meeting. For further details on the outcome of the screening of the Oral Declaration(s) of Interest made at the beginning of the meeting, please refer to the Annex.

4. Chemical database and plant identification brief update

The Working Group (WG) was given a quick update on the status of plant characterisation work. Almost 90% of work has been completed. Ten meetings with experts were already held since the beginning of the year and five more are planned until the end of August 2022.

Justyna Slodek-Wahlstrom and Klara Nicova will leave EFSA at the end of August 2022, therefore Eirini Kouloura will take over the plant characterisation work in September.

5. Toxicity characterisation of plant-based substances – experimental data

The contractor updated the WG on the progress of the extensive literature review to characterise the toxicity of substances of possible concern. The majority of the original 1000+ substances have been processed by the contractor and are ready for EFSA's validation.

6. Toxicity predictions - Methodological considerations

When literature data are available, they will be prioritised in the database, with QSAR predictions being reported only for substances/hazard classes without experimental data. The WG discussed strategies for presenting QSAR data and for solving potential conflicting outcomes between QSAR models. It was suggested to consider alignment with the OECD QSAR Toolbox in terms of abbreviations and layout. The strategy will also be discussed with the iDATA Unit of EFSA to align with other QSAR models employed. For the genotoxicity hazard class, the WG on Genotoxicity of EFSA will be consulted for advice during their upcoming meeting on 27th of June regarding the proposed approach to assess genotoxicity QSAR data.

7. Next meeting

- 1 September 2022, 9:30-12:30, 14:00-17:00 (MS Teams meeting)



Methodology & Scientific Support Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 4 April 2022, online

(Agreed on 20 April 2022)

Participants

- Working Group Members: Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye¹
- EFSA:
 - MESE Unit: Alexis Nathanail (Chair), Klara Nicova
 - KNOW Unit: Melina Steinbach

1. Welcome and apologies for absence

The Chair welcomed the participants. No apologies for absence were received.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

¹ Participated in agenda points 5-7.

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

4. Chemical database - clean-up of chemical identifiers

The Working Group (WG) discussed the outcome of an exercise to address any inconsistencies within the database in terms of chemical identifiers and chemical names.

5. Toxicity characterisation of plant-based substances – toxicity predictions

The WG reviewed action items from the last WG meeting. The WG discussed the methodology for combining the predictions from the two QSAR systems (VEGA and DK-DB) to reach consensus results. It was decided that there will be at least 3 classes for QSAR outcomes: positive, equivocal and negative. However, the process for arriving at each outcome will be determined for each endpoint separately due to differences in the nature of the endpoints and the different models available. Furthermore, in some cases the models are complementary to each other, therefore it is not always possible to expect all the models to reach the same conclusion. The discussion on the criteria for reaching a QSAR outcome will be continued in the next WG meetings.

6. Next meetings

- 7 June 2022, 9:30-12:30, 14:00-17:00 (Teams meeting)
- 1 September 2022, 9:30-12:30, 14:00-17:00 (Teams meeting)



SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 23 February 2022, online

(Agreed on 15 March 2022)

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye
- EFSA:
MESE Unit: Alexis Nathanail (Chair), Klara Nicova
KNOW Unit: Bernard Bottex, Melina Steinbach
- External Contractor:
ECOMOLE: Krystof Dibusz¹

1. Welcome and apologies for absence

The Chair welcomed the participants. No apologies for absence were received.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence² and the Decision of the Executive Director on Competing Interest Management³, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues

¹ Participated in agenda point 4.

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

³ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Toxicity characterisation of plant-based substances – experimental data

Krystof Dibusz informed the Working Group (WG) about the progress of the extensive literature review to characterise the toxicity of substances of possible concern. The majority of the original 1000+ substances have been already pre-coded by the contractor and are ready for EFSA's validation. In addition, approximately 170 new substances from the validated plants were added to the Chemcombo platform. Their literature searches have been performed and the substances are ready for screening.

5. Toxicity characterisation of plant-based substances – toxicity prediction

Emilio Benfenati presented the results of the VEGA model. Toxicity predictions have been made for the following endpoints: acute toxicity (rat LD50), genotoxicity, mutagenicity, carcinogenicity, developmental and reproductive toxicity, endocrine activities (estrogen, androgen, thyroid, steroidogenesis modalities) and hepatotoxicity. Cardiotoxicity and nephrotoxicity models are still being developed.

Eva Bay Wedeby introduced the WG to the methodology used for retrieving predictions from the Danish QSAR Database (DK-DB). First, SMILES and CAS combinations were checked for each of the 1000+ substances. In total, 605 substances were found in the DK-DB and the predictions incorporated into the Masterfile. Furthermore, The DK-DB also includes information on CLP classifications. To date, 93 REACH-registered substances have been found in the Compendium. It was agreed that the regulatory information (e.g. REACH/CLP) will take priority before the results from the literature review and the *in silico* predictions. The prioritisation of results in the database will be the following: regulatory information > experimental results > QSAR predictions > read-across.

6. Any Other Business

It was agreed that a thorough data cleaning will be necessary, for any duplicates or inconsistencies in chemicals' identifiers that may be present.

7. Next meetings

- 4 April 2022, 9:30-12:30, 14:00-17:00 (Teams meeting)
- 7 June 2022, 9:30-12:30, 14:00-17:00 (Teams meeting)



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

CUMULATIVE MINUTES OF THE MEETINGS OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS HELD IN 2021

(Agreed on 07 January 2022)

Participants

- Working Group Members:
Robert Anton, Ulla Beckman-Sundh, Carlo Bicchi, Qasim Chaudhry, Massimo Collino, Wirginia Kukula-Koch, Kirsten Pilegaard, Mauro Serafini and Luigi Milella
- External Contractors:
ECOMOLE: Krystof Dibusz
- EFSA:
SCER Unit: Bernard Bottex and Justyna Slodek Wahlstrom

1. Adoption of agenda

Due to the specific and similar format of the meetings (one-to-one meetings between each expert and EFSA staff to review plants assigned), no formal agenda was drafted. See Note below for further details.

2. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

3. Scientific topic(s) for discussion

NOTE: As agreed a priori with the hierarchy, due to the format as well as the repetitive nature of the WG Compendium of Botanicals meetings on plant review (always one-to-one meetings between expert and EFSA staff to review the work done on plant review), minutes for single meetings have been replaced by one single document summarising all the meetings held in 2021 and describing briefly the work carried out in 2021 on plant review part. These cumulative minutes of the meetings shall be approved by the working group members and published after the end of the year. Hence, they fall under SOP 005 as an ex-ante agreed exception, and do not constitute a non-conformity.

Over the last six years, the activities of the EFSA WG on Compendium of Botanicals focused on transforming the initial Excel file into a web-accessible user friendly database, increasing the number of plants in the Compendium to around 2600 species, and improving the quality of the information provided on composition, toxicity and adverse effects by means of an extensive search of the literature for the plants considered.

Next to the parallel ongoing toxicity characterisation work documented in its own minutes, WG activities on plant review were focused on validation of the composition/toxicity information retrieved for around 891 white list plant species and coding of the relevant information. The aim was to make the data ready to be transferred to the EFSA database.

To fulfil the above objective, 22 bilateral meetings were held for the review of the plants in the course of 2021. The rate of review of plants in the WG assessment in 2021 was on average 240 plants in 6 months. During these meetings, EFSA staff met with each of the experts to review the literature and code the relevant information on each plant species both in terms of composition of the substances of concern and toxicity. Altogether 555 white list plants were screened and coded and 336 white list plants plus 20 yellow list plants are still left for review at the end of 2021.

Please refer to Annex 1 for further details on meeting dates and experts participation.

Due to Covid-19 pandemics, all meetings took place in the form of webconferences.

4. Next meeting(s)

As the project will continue over the next two years, another series of meetings for the validation of the remaining plant species will be organised in 2022 in the same format.

Annex I

11-Feb-21	11-Feb-21	WG Botanicals - Plant review- Wirginia Kukula Koch
16-Feb-21	16-Feb-21	WG Botanicals - Plant review– Qasim Chaudhry
24-Feb-21	25-Feb-21	WG Botanicals - Plant review– Ulla Beckham
03-Mar-21	04-Mar-21	WG Botanicals - Plant review– Kirsten Pilegaard
18-Mar-21	19-Mar-21	WG Botanicals - Plant review– Robert Anton
12-Apr-21	19-Apr-21	WG Botanicals - Plant review– Massimo Collino
28-Apr-21	29-Apr-21	WG Botanicals - Plant review– Carlo Bicchi
05-May-21	05-May-21	WG Botanicals - Plant review– Mauro Serafini
12-May-21	12-May-21	WG Botanicals - Plant review– Robert Anton
26-May-21	27-May-21	WG Botanicals - Plant review– Robert Anton
08-Jun-21	08-Jun-21	WG Botanicals - Plant review– Mauro Serafini
10-Jun-21	11-Jun-21	WG Botanicals - Plant review– Wirginia Kukula Koch
22-Jun-21	22-Jun-21	WG Botanicals - Plant review– training Luigi Milella
28-Jun-21	29-Jun-21	WG Botanicals - Plant review– Kirsten Pilegaard
20-Sep-21	21-Sep-21	WG Botanicals - Plant review– Carlo Bicchi
13-Oct-21	14-Oct-21	WG Botanicals - Plant review– Kirsten Pilegaard
28-Oct-21	29-Oct-21	WG Botanicals - Plant review– Carlo Bicchi
10-Nov-21	11-Nov-21	WG Botanicals - Plant review– Mauro Serafini
29-Nov-21	30-Nov-21	WG Botanicals - Plant review– Massimo Collino
09-Dec-21	10-Dec-21	WG Botanicals - Plant review– Wirginia Kukula Koch
16-Dec-21	17-Dec-21	WG Botanicals - Plant review– Luigi Milella
21-Dec-21	21-Dec-21	WG Botanicals - Plant review– Robert Anton



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 22 November 2021, online

(Agreed on 16 December 2021)

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye
- External Contractors:
ECOMOLE: Krystof Dibusz
- EFSA:
SCER Unit: Bernard Bottex (Chair), Alexis Nathanail

1. Welcome and apologies for absence

The Chair welcomed the participants and in particular Alexis Nathanail who will take over the coordination of this activity in 2022, following EFSA's reorganisation. A transition period is foreseen to ensure adequate hand-over of the activity.

2. Adoption of agenda

The agenda was adopted without any modification.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Toxicity characterisation of plant-based substances – experimental data

Krystof Dibusz informed the participants about the successful transfer to EFSA of the information (composition and toxicity/adverse effects) for around 2200 plant species. Request was made to prioritise the validation of the remaining 400+ plant species so that the list of the substances of possible concern for human list, for which the toxicity characterisation is needed, can be finalised.

Participants were informed about the progress of the extensive literature review to characterise the toxicity of the substances of possible concern (gathering of existing information/experimental data). The search has been done for around 700 substances and 350 are ready for EFSA's validation of the information pre-coded by the Contractor. Mistakes on the identifiers have been evidenced for 60 substances. The list will be forwarded to EFSA for correction.

5. Toxicity characterisation of plant-based substances – toxicity prediction

The working group reviewed the outcome of the toxicity prediction for 55 test substances for the following endpoints:

5.1. Mutagenicity

Three prominent free-access systems are available for AMES test predictions (VEGA, DK EPA and TEST), which allows to define three levels of reliability (high/medium/low) depending on the number of systems agreeing with each other. In case of low reliability, read-across will be considered for possible additional information;

For *in vivo* micronucleus predictions, only two systems are available (DK EPA and VEGA); 27 out of the 55 substances are predicted by the two systems. Results for substances that are predicted only by one of the two systems should also be considered but with a lower reliability, together with the read-across results.

For the prediction of chromosomal aberration, both VEGA and DK EPA are using the same models (lung + ovary). The issue of how to aggregate the results of the models needs to be further discussed.

It was reminded that EFSA's decision tree for mutagenicity testing requires a stepwise approach:

- Step 1: AMES test + *in vitro* micronucleus test
- Step 2, if one of the step 1 tests is positive: *in vivo* micronucleus test and chromosome aberration test.

The predictions for the *in vitro* micronucleus test will be retrieved for the 55 test substances for the next meeting.

5.2. Developmental and reproduction toxicity

Two systems (DK EPA and Janus) are available. Results will be considered when at least two models provide consistent results.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

5.3. Liver toxicity

DK EPA system predicts liver toxicity related to carcinogenicity, while VEGA has only one model for liver toxicity (non-carcinogenicity) predictions.

5.4. Nephrotoxicity, cardiac toxicity

The models for these endpoints are not implemented yet in VEGA and do not exist in the other systems. Their implementation in VEGA is foreseen in January/February 2022.

5.5. Endocrine activity

Only models predicting estrogenic, androgenic, thyroid and steroidogenesis modalities are of interest for this project. Results for sub-modalities (e.g. interaction with estrogen receptor alpha vs. interaction with estrogen receptor beta) will be combined.

5.6. Carcinogenicity

None of the 55 test substances are in agreement between the systems used (Janus and DK EPA). It was explained that the DK EPA system is designed for carcinogenicity labelling purpose and as such should not lead to false positives. Moreover, it contains a filter for genotoxicity, which should be deactivated, as the purpose of this activity is to predict carcinogenicity, independently whether it is associated or not with genotoxicity. The test for carcinogenicity prediction will therefore be re-run, integrating the new results obtained from the DK EPA system following this re-parameterisation.

5.7. Acute toxicity

The predictions for acute toxicity for the 55 test substances are missing and will be generated for the next meeting. It was reminded that the working group is only interested in LD50 values in rats, via oral exposure, and with values lower or equal to 2000 mg/kg.

Although EFSA is only interested in positive results because of the hazard identification nature of the Compendium, negative results will also be captured to improve existing QSAR models and read-across models

In view of the difficulty to obtain conclusive prediction results from QSAR models for some of the endpoints, and anticipating the frequent need for additional read-across information, an automatic tool will be developed to identify possible structural alerts for the substances and endpoints considered. A couple of months will be needed for its implementation. Priority will be given to the carcinogenicity endpoint, considering the absence of results with the available QSAR models.

6. Next steps

For the next meeting in February 2022, one single file will be generated for the 1100+ substances and endpoints of interest (1 endpoint per Excel sheet). Each Excel sheet should provide the consensus prediction for the endpoint considered for each system, as well as the prediction (if in the applicability domain) of each model of the system. A file with the results of the read-across will also be prepared.

The objective is to have a better idea on the number of substances and endpoints for which it is possible to conclude directly on the toxicity based on the outcome of the QSAR/read across prediction, and the number of substances and endpoints for which no conclusion could be reached and that will be subject to a further analysis of the information available by the experts of the working group.

7. Next meeting(s)

- 23 February 2022, 9:30 – 12:30 and 14:00 – 17:30 (Teams meeting)



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 6 and 7 September 2021, online

(Agreed on 30 September 2021)

Participants

■ Working Group Members:

Eva Bay Wedebye, Ulla Beckman Sundh, Emilio Benfenati, Carlo Bicchi, Qasim Chaudhry, Massimo Collino, Wirginia Kukula-Koch, Luigi Milella, Kirsten Pilegaard, Mauro Serafini

■ External Contractors:

ECOMOLE: Krystof Dibusz

■ EFSA:

SCER Unit: Bernard Bottex (co-Chair), Justyna Slodek-Wahlström (co-Chair), Anna Steinbach

NUTRI Unit: Eirini Kouloura

1. Welcome and apologies for absence

The Chair welcomed the participants to this “interim meeting” aiming at reviewing the progress made and the work still to be done for the finalisation of the Compendium of Botanicals. As the last meeting bringing the whole working group together took place in November 2019, the Chair organised a tour de table so that the new members who joined the group after that date can introduce themselves. Apologies were received from Prof. Robert Anton.

2. Adoption of agenda

The agenda was adopted without any modification.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Compendium of Botanicals – Plant validation

The working group was updated on the status of the plant composition review for the last batch of 891 plants. Overall, a total of 493 plants are still to be validated, which is anticipated to take an extra 13 months assuming the WG is to continue at the current rhythm of work.

Participants were informed that the transfer of all the plants validated so far is still pending due to a problem at EFSA DATA level. The consequence is that public has only access to the microstrategy reports describing the Compendium available in 2015, i.e. before the listed plant species were subject to an extensive search of the available literature. As a temporary solution, the Contractor has developed a "Plant Viewer" tool allowing interested parties to access the current content of the COMBO Platform, i.e. plants species with validated data but also species for which the data validation is still pending or ongoing. As it is still not possible to tell when the data transfer issue will be fixed, the link to the Plant Viewer will be inserted on the EFSA Website, together with an explanatory text on how to use the tool and interpret the information it contains.

5. Compendium of Botanicals – substance toxicity characterisation

Participants were updated on the second phase of the project that has started in 2020, i.e. the toxicity characterisation of the 1100+ substances flagged so far as "of possible concern for human health" (substances containing (a) chemical group(s) considered as of concern by default by the working group).

The work done with the plant validation has shown that a minority of these substances have been tested for possible toxicity, whereas most of these substances have only been subject to analytical chemistry. A methodology combining retrieval of existing information and toxicity prediction was therefore agreed:

- Retrieval of existing experimental toxicity data by the Contractor:
 - From EFSA OpenFoodTox database;
 - From the literature, cross-checking the results with the information in PubChem/ChemID+;
- Toxicity prediction for a limited list of endpoints (see section 5.2) using a stepwise approach:
 - QSAR modelling with VEGA, US-EPA T.E.S.T. and the Danish (Q)SAR database;
 - Read-across in case the above-mentioned QSAR models lead to diverging conclusions re. the toxicological endpoint considered. A weight of evidence approach will then be used to integrate the various information retrieved and to reach a conclusion;

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

5.1. Identifying existing information

The Contractor presented the [CHEMCOMBO platform](#) developed for the screening of the information retrieved from the literature for the substances of possible concern. Although the design has changed compared to the COMBO Platform used for the plant validation, the functionalities and coding fields remain unchanged, as demonstrated during the meeting with the case studies presented to illustrate the various situations that the working group will be confronted with (data rich vs. data poor). A PowerPoint presentation guiding the users on how to connect and screen a substance step-by-step will be shared with the working group.

The contractor informed the participants that 500 substances are now ready to be validated. Batches of 10 substances will be distributed among the working group members. Once they have been screened, they will be reviewed together with the batches of plants to be validated during one-to-one meetings with EFSA Secretariat. A meeting with the whole working group will then be organised in 2022 to share experience and good practice among the participants.

5.2. Toxicity prediction

QSAR modelling and read-across will be used to try and predict toxicity for the following endpoints:

- Acute toxicity
- Genotoxicity
- Carcinogenicity
- Mutagenicity
- Developmental and reproductive toxicity
- Hepatotoxicity
- Nephrotoxicity
- Cardiac toxicity
- Endocrine activity (oestrogenic, androgenic, thyroid and steroidogenic modalities)

A number of criteria related to applicability domain of the models, reliability and/or similarity were also agreed in order consider the outcome of a prediction as valid.

The outcome of mutagenicity prediction for 57 test substances was presented; the three QSAR systems were in agreement for 38 substances and in disagreement for 1; these results were considered as promising, although it should be noted that the mutagenicity is one of the endpoints with the best models. A consensus analysis on the other above-mentioned endpoints for the same 57 test substances will be done for November.

5.3. Integration of the various information

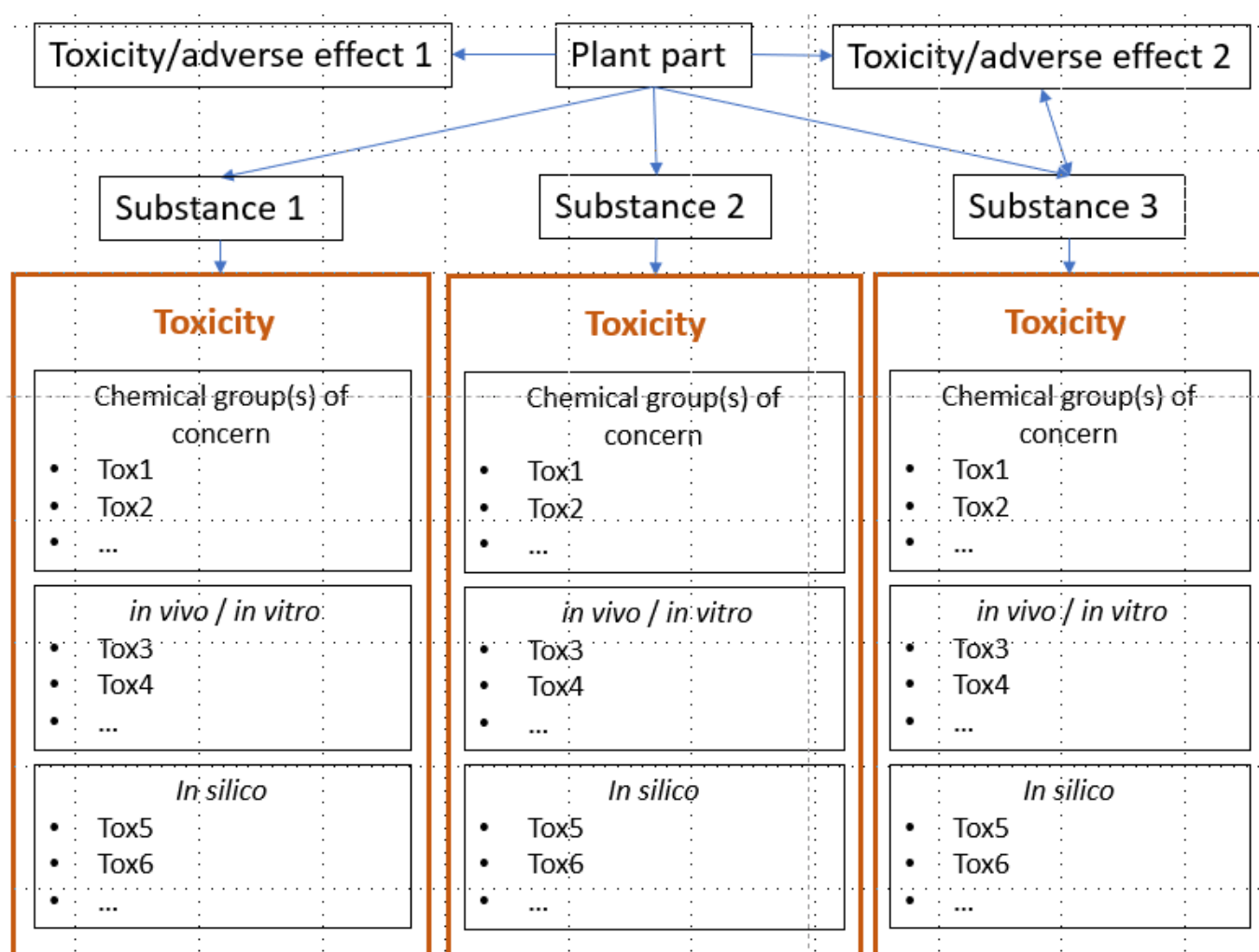
The working group discussed what to do with substances for which there is no relevant information on toxicity in the literature, and for which predictive toxicity gives only negative or inconclusive results for the endpoints of interest. Decision was made that these substances should still be flagged as of possible concern for human health on the basis that they contain (a) chemical group(s) of concern. The working group will review the list of 118 chemical groups considered as of concern by default and ensure that a rationale for the concern is given for each group.

5.4. Transfer and display of the results

The first part of the project dealing with plant species resulted in the coding of relevant information from the literature search into three datasheets ("composition", "endpoint" and "genotoxicity"), making use of the existing EFSA catalogues.

The second phase of the project dealing with substances toxicity characterisation requires coding of toxicity information retrieved from the literature following the same scheme/structure ("endpoint" and "genotoxicity") previously mentioned, but also coding of the results and conclusions from the toxicity prediction (so far captured in an Excel file). As soon as a full set of results is available for a given substance, contact will be made with the EFSA DATA Unit to discuss the best way to format/store these data.

The question of how to display the results on the EFSA website was also briefly discussed, considering that at the end of the project, the following information will be available for a given plant part (note that a plant may have information for more than one plant part ...):



This point will be further discussed at the next meeting of the working group. EFSA will also contact colleagues from DATA to identify possible options.

6. Next steps

Working group members will continue with the validation of their plants batches (using the COMBO platform) and will start reviewing toxicity information related to the specific substances (using the CHEMCOMBO Platform).

The list of chemical groups considered as of concern by default will be updated and reviewed.

QSAR toxicity predictions for the identified endpoints of interest will be provided first for the 57 test substances and then for the remaining 1100 compounds.

7. Any other Business

The working group was given an update of the status of plant-based Traditional Foods submitted to the EFSA NUTRI Unit and was invited to contribute to the assessment of *Clitoria ternatea* notification by screening the top 100 relevant articles referring to the specific plant part, flowers and extracting the information relevant to compounds of concern, toxicity data, absence of toxicity and allergenicity.

8. Next meeting(s)

One-to-one meetings will be organised until the end of the year to review the relevant composition and toxicity/adverse effects information for plants, as well as toxicity information retrieved for specific substances of possible concern for human health. A meeting with the whole working group will be organised early 2022 (date to be determined) to review experience with the CHEMCOMBO platform.

The subgroup dealing with toxicity prediction methodology will meet on 22 November 2021, from 9.30 to 12.30, and from 14.00 to 17.00, to review the consensus analysis made for the 57 test substances.



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 2 July 2021, online

(Agreed on 27 August 2021)

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry, Eva Bay Wedebye
- External Contractors:
ECOMOLE: Krystof Dibusz, Klara Nicova
- EFSA:
SCER Unit: Bernard Bottex (Chair)

1. Welcome and apologies for absence

The Chair welcomed the participants and in particular Dr. Eva Bay Wedebye from the Technical University of Denmark who joined the working group for her expertise on the Danish EPA QSAR system.

2. Adoption of agenda

The agenda was adopted without any modification.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Toxicity characterisation of plant-based substances – experimental data

The working group was informed that the first batch of 300 substances is now ready for the validation of the collected information by the working group. The scientific literature was searched for experimental toxicity data or reported adverse effects and what was considered relevant information pre-coded by the Contractor.

A presentation of the new platform (chemcombo.ecomole.com), highlighting new features, will be prepared for the September meeting, and a couple of substances will be used to illustrate / train the working group members on how to use this new platform.

In preparation of the meeting, the following improvements will be made to the platform:

- Update the list of the assignees
- Red lines visible next to the title of the articles for which information has been coded.
- Check whether epidemiological studies is in the EFSA catalogue of toxicological tests and make it then visible. If not, consider using "other" as backup solution
- Send the Secretariat the Excel list of the 300 substances ready for screening.
- Create a system to store the substances for which "no evidence for toxicity could be identified, either from the literature, or when trying to predict the toxicity using QSAR models and read across; still, these substances may be of concern because of structural features". The wording of the previous sentence will be discussed at the next meeting of the working group

Moreover, the following actions were identified:

- Update the list of chemical groups of concern by default and ensure that the reason for the concern has been reported

It was confirmed to the Contractor that photogenotoxicity should be considered for the Compendium, when resulting from oral route of exposure. Topical photogenotoxicity will not be considered. *In vitro* data on anticoagulant activity and haemolysis tests will also be considered as relevant information.

It was also suggested to use the ECHA REACH/CLP information as a help when it is no possible to conclude on an endpoint based on the literature search (no experimental data found) or the predictive toxicity results (results of the various models and read-across are inconclusive). Additional ECHA data could then be used as additional information for the weight of evidence approach to decide on the conclusion for the endpoint considered. The Contractor reported that they have a system in place to automatically search the ECHA database.

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

5. Toxicity characterisation of plant-based substances – toxicity prediction

DK EPA: using CAS numbers only, around 500 substances have been found with predicted values. It was clarified that the identifiers have already been checked for the 1100 substances of interest of this project, and as such, the search can be done using any type of identifier (e.g. SMILES) to refine the number of structures covered by the DK EPA QSAR system. The predictions for the below-mentioned endpoints of interest and the corresponding DK EPA self-classification will be extracted for the 57 priority compounds by end of August. The following approach will be followed:

- 1/ structure checks
- 2/ extraction of the predictions in 1-go
- 3/ deletion of the predictions when the substance falls outside the applicability domain of the model

The working group was reminded about the endpoints of interest

- LD50 (≤ 2000 mg/kg) in rats via oral route
- Genotoxicity
- Carcinogenicity
- Mutagenicity
- Developmental and reproductive toxicity
- Hepatotoxicity
- Nephrotoxicity
- cardiac toxicity
- Endocrine activity (oestrogenic, androgenic, thyroid and steroidogenic modalities)

The importance of stressing to the users that these information refer to the properties (hazards) of the substance, and do not necessarily imply risks was reminded.

The rules for considering the prediction results as relevant are the following:

- 0/ no experimental data available for the endpoint considered
- 1/ the substance should fall in the applicability domain of the model
- 2/ the reliability of the prediction will be considered; it was reminded that for VEGA, a consensus ≥ 0.5 or a reliability ≥ 0.7 is requested. For TEST, results with reliability values between 0.35 and 0.65 are excluded.
- 3/ in case of diverging results between models, read-across will be used; the threshold for similarity has been set to 0.85

A consensus analysis will be performed by Emilio for the September meeting, after the results from EVA have been received, to get an idea of how many substances can still not be sorted out after applying these four steps,

The adequacy of the above-mentioned cut-off values for consensus, reliability and similarity, as well as the issue of how to integrate the results from the different QSAR systems remain pending and will be discussed after the predictions from the various systems have been compiled together, i.e. at the next meeting of the working group in September.

Dr. Huixiao Hong, Chief of the Bioinformatics Branch of the US FDA presented the models available for endocrine activity, genotoxicity, carcinogenicity and hepatotoxicity as well as the artificial

intelligence systems developed for the predictions. It was clarified that before adding these models to the methodology adopted by this working group, additional publicly available information should be received from the US FDA on:

- the models used and their applicability domains
- a description on how they were made and tested (size of the training sets, chemical classes used, eventual cross-validation)
- the prediction confidence (confidence thresholds for the various models)

6. Next steps

The following actions were agreed:

1/ ChemCombo Platform:

- Send the Secretariat the Excel list of the 300 substances ready for screening.
- Update the list of the assignees
- Red lines visible next to the title of the articles for which information has been coded.
- Check whether epidemiological studies is in the EFSA catalogue of toxicological tests and make it then visible. If not, consider using "other" as backup solution
- Create a system to store the substances for which no evidence for toxicity could be identified
- Send the Secretariat the updated list of chemical groups of concern that have been coded

2/ Toxicity predictions

- Secretariat to circulate the master file for the fixed numbering of the 57 substances
- Emilio and Eva to insert the prediction results on the Excel Masterfile, using one spreadsheet per endpoint, and having removed the result out of the applicability domain of the models
- Emilio to prepare a consensus analysis for the next meeting
- Secretariat to go back to the US FDA asking for further information on the models that they are using

7. Next meeting(s)

- 6-7 September 2021, starting at 14.00 on the 6th and finishing at 17.00 on the 7th –Teams meeting with the whole working group.
- 22 November 2021, 9.30-12.30, 14.00 -17.00 – Teams meeting



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 28 April 2021, online

(Agreed on 4 May 2021)

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry
- External Contractors:
ECOMOLE: Krystof Dibusz, Klara Nicova
- EFSA:
SCER Unit: Bernard Bottex (Chair)

1. Welcome and apologies for absence

The Chair welcomed the participants who were informed about the ongoing process for adding an expert of the Danish EPA QSAR system in the working group. The importance for the methodology of this project of adding the information from a third QSAR system (next to VEGA and TEST) was acknowledged, as it will bring more confidence in the QSAR consensus prediction results.

2. Adoption of agenda

The agenda was adopted without any modification.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Toxicity characterisation of plant-based substances – experimental data

The working group reviewed the methodology applied for the screening of the literature and questions resulting from the searches made for the first 50 substances. The following decisions were made:

- The reviewer is looking at the TOP50 articles; if relevant articles are found, the full texts are retrieved and data extracted/coded. ChemID Plus is then consulted to check if more toxicity endpoints than those identified with the literature search are associated with the substance considered.
- If no relevant article is identified in the TOP50, a manual search of the whole articles' dataset will be performed using the toxicity-related keywords. If the dataset contains more than 1000 articles the name(s) of the substance AND the toxicity-related keywords will be used.
- It was reminded that the working group is interested in *in vivo* data resulting from oral intake, except for digestive enzyme inhibition, genotoxicity, and endocrine activity, for which *in vitro* data will be considered as relevant.

The Contractor was reminded about the June 2021 deadline to deliver the results of the review for the first 300 substances.

5. Toxicity characterisation of plant-based substances – toxicity prediction

The working group was reminded about the endpoints of interest

- LD50 (≤ 2000 mg/kg) in rats via oral route
- Genotoxicity
- Carcinogenicity
- Developmental and reproductive toxicity:
- Hepatotoxicity, nephrotoxicity, cardiac toxicity
- Endocrine activity

The importance of stressing to the users that these information refer to the properties (hazards) of the substance, and do not necessarily imply risks was reminded.

Three QSAR systems (VEGA, TEST and DK EPA) will be used for this project to consider as many prediction models as possible and as such, compensate for the limitations of the models when taken in isolation. To allow for comparison of the predictions from the various systems, the following criteria were agreed:

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

- VEGA: consensus score ≥ 0.5 , or reliability score ≥ 0.7
- TEST: exclude results with reliability between 0.35 and 0.65
- DK EPA: keep only results “in the prediction domain” of the model

In case QSAR models lead to conflicting conclusions, information from read-across will be considered in a weight of evidence approach. To be taken into account, the working group agreed that the threshold for similarity should be ≥ 0.85 .

6. Next steps

The review of the information from the literature review (experimental data on toxicity) and from QSAR/read-across (predictive toxicity) will be performed in parallel. These activities should not slow down the other activity of the working group (validation of the composition/toxicity information for the last group of 900 plants)

The following actions were agreed:

- The Secretariat will follow-up with the US FDA and ask about possible models for hepatotoxicity, nephrotoxicity, and cardiac toxicity prediction
- Endocrine activity QSAR models will be added to the table.
- Results from TEST, VEGA and NCSTOXVega not complying with the consensus/reliability thresholds criteria will be removed from the table
- Results from read-across / structural alert models will be added. Those not complying with the threshold for similarity criterion will be taken out.

7. Next meeting(s)

- 2 July 2021, 9.30-12.30, 14.00 -17.00 – Teams meeting
- 6-7 September 2021, starting at 14.00 on the 6th and finishing at 17.00 on the 7th – Physical or Team meeting with the whole working group.
- 22 November 2021, 9.30-12.30, 14.00 -17.00 – Teams meeting



Scientific Committee and Emerging Risk Unit

SCIENTIFIC COMMITTEE

MINUTES OF THE MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 3 February 2021, online

(Agreed on 16 February 2021)

Participants

- Working Group Members:
Emilio Benfenati, Qasim Chaudhry
- Hearing Experts:
National Food Institute (DK): Nikolai Nikolov, Eva Wedebye
- External Contractors:
ECOMOLE: Krystof Dibusz
- EFSA:
SCER Unit: Bernard Bottex (Chair)

1. Welcome and apologies for absence

The Chair welcomed the participants and particularly Dr. Emilio Benfenati who joined the working group at the beginning of 2021. A short summary of the EFSA activities was provided to him.

2. Adoption of agenda

The agenda was adopted without any modification.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Toxicity characterisation of plant-based substances

During the first part of the project, around 1100 plant-based substances have been identified as of possible concern for human health, on the basis that they contain one or more chemical group(s) considered as of concern by default (e.g. alkaloid, saponin, epoxide etc). The purpose of this meeting was to agree on a strategy to characterise the actual toxicity of these substances.

The Working Group agreed on the following endpoint for the toxicity characterisation:

- Acute toxicity (LD50) – relevant only if LD50 in rats \leq 2000 mg/kg
- Genotoxicity: the EFSA scientific opinion on genotoxicity strategies applicable to food and feed safety assessment (<https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2011.2379>) recommends a stepwise approach:

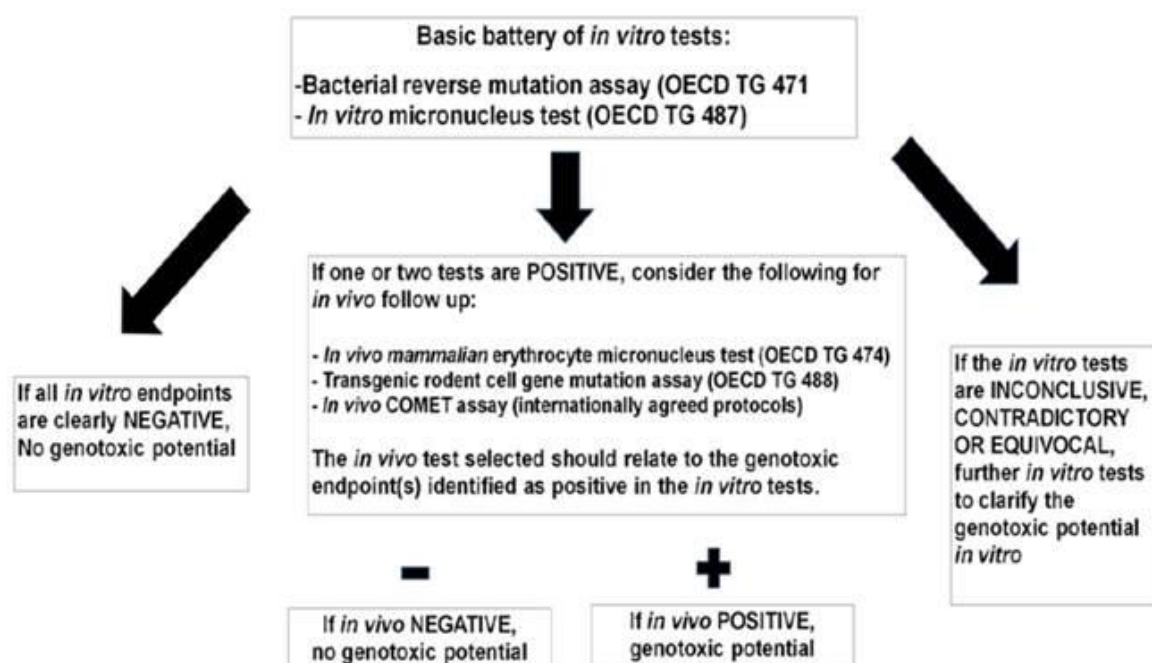


Figure 1. Schematic representation of the genotoxicity testing strategy recommended by the EFSA Scientific Committee

Following discussion with EFSA Staff coordinating the EFSA cross-cutting working group on genotoxicity, it was clarified that the chromosomal aberration model is not needed if we have models for both *in vitro* and *in vivo* micronucleus tests, since they detect both structural and numerical chromosome changes, while chromosomal aberration tests (TG 473 and TG475) can detect structural

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

chromosome aberrations only. If we have model(s) for the *in vivo* chromosomal aberration test (OECD TG 475), these can be used for step 2 (i.e. if the AMES test and/or the *in vitro* micronucleus test is/are positive). The working group should check if VEGA, TEST and DK-EPA QSAR systems contain models for the transgenic rodent cell gene mutation assay and for the COMET assay. The EFSA colleagues recommended to be careful with models predicting *in vivo* endpoint, since their predictive ability is not very high (e.g. see <https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2019.EN-1598>).

- Carcinogenicity: binary result
- Developmental and reproductive toxicity
- Hepatotoxicity and nephrotoxicity

The working group agreed on the following stepwise approach:

1. Check if the substance has already been assessed

The EFSA OpenFoodTox database (<https://www.efsa.europa.eu/en/microstrategy/openfoodtox>) will be used to check if the substance has already been assessed by EFSA. The content of the database as well as the related opinion(s)/reference(s) will be reviewed for possible information on the endpoints of interest.

2. Search for possible toxicity data

For those substances not present in OpenFoodTox, an extensive literature search will be performed, using the substance name and prioritising the retrieved articles with the toxicity-related keywords used in the first phase of the project. The Top50 articles will then be screened for possible relevant information. The outcome of the search will be compared with the toxicity information available in Pubchem for that substance. Should Pubchem contain toxicity endpoints not identified in the Top50 articles, the rest of the retrieved articles will be searched for possible information on these endpoints.

3. Toxicity predictions

QSAR models and read-across will be used to predict toxicity in case of absence of experimental data. Three different systems will be used for QSAR: VEGA (Mario Negri Institute), the DK-EPA models, and TEST (US EPA).

Results will be considered only when the substance is in the prediction domain of the model and when the consensus score is greater than or equal to 0.5, or the reliability score is greater than or equal to 0.7. If models complying with these rules give diverging conclusions, read-across will be considered, as long as the similarity criteria is greater than or equal to 0.9. The outcome of QSAR models and read-across will then be considered in a weight of evidence approach to conclude on the endpoint considered (based on the valid results).

For mutagenicity and carcinogenicity endpoints, the Begnini/Bossa rules for botanicals will be used in case of doubt.

For developmental and reproductive toxicity, two models are implemented (CAESAR and P&G); the reliability of the results can be described as low, medium or good. It was agreed that to be considered, at least one model prediction should have a "good" reliability.

For hepatotoxicity and nephrotoxicity, the databases on which the models are built are very weak, and it is likely that the results will come as "out of the prediction domain" or "not reliable". It was mentioned that the US FDA may have some models for hepatotoxicity, nephrotoxicity and cardiac toxicity but their performance needs to be reviewed. It was clarified that when the predictive toxicity tools are inconclusive for some substances and/or endpoints, this shall be reflected in the EFSA compendium.

5. Next steps and timeframe

- The list of the 1100 substances with all pubchem identifiers will be provided after chemical groups and inorganic compounds have been removed. VEGA and TEST, and read-across where appropriate will then be run for these substances and endpoints of interest.
- EFSA will further discuss with the Danish National Food Institute whether they could run the substances on the DK-EPA QSAR models.
- The screening of the literature for the other substances not present in OpenFoodTox shall proceed from now on; The working group will be informed as soon as the literature has been screened for the first 50 substances so that the overall approach for toxicity characterisation can be tested. The 50 substances should be representative of the various cases the working group will encounter (already assessed by EFSA, not assessed yet but experimental data available for some of the endpoints of interest, no experimental data available).
- EFSA will contact FDA and ask for additional information on the models they have for hepatotoxicity, nephrotoxicity and cardiac toxicity.

6. Next meeting(s)

- 28 April 2021, 9.30-12.30, 14.00-17.00 – Teams meeting
- 2 July 2021, 9.30-12.30, 14.00-17.00 – Teams meeting
- 22 November 2021, 9.30-12.30, 14.00-17.00 – Physical or Teams meeting



SCIENTIFIC COMMITTEE

CUMULATIVE MINUTES OF THE MEETINGS OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS HELD IN 2020

(Agreed on 23.12.2020)

Participants

■ Working Group Members:

Robert Anton, Ulla Beckman-Sundh, Carlo Bicchi, Qasim Chaudhry, Massimo Collino, Wirginia Kukula-Koch, Kirsten Pilegaard, Mauro Serafini and Vittorio Silano

■ External Contractors:

ECOMOLE: Krystof Dibusz, Pavla Vejvodova

■ EFSA:

SCER Unit: Bernard Bottex and Justyna Slodek Wahlstrom

1. Adoption of agenda

Due to the specific format of the meetings (one-to-one meetings between each expert and EFSA staff to review work progress), no formal agenda was drafted. See Note below for further details.

2. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence¹ and the Decision of the Executive Director on Competing Interest Management², EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

3. Scientific topic(s) for discussion

NOTE: As agreed a priori with the hierarchy, due to the format as well as the repetitive nature of the WG Compendium of Botanicals meetings that took place in 2020 (always one-to-one meetings between expert and EFSA staff to review the work done), minutes for single meetings have been

¹ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

² http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

replaced by one single document summarising the meetings held in 2020 and describing briefly the work carried out. These “summary minutes” shall be approved by the working group members and published at the end of the year. Hence, they fall under SOP 005 as an ex-ante agreed exception, and do not constitute a non-conformity.

Over the last five years, the activities of the EFSA WG on Compendium of Botanicals focused on transforming the initial Excel file into a web-accessible user friendly database, increasing the number of plants in the Compendium to around 2600 species, and improving the quality of the information provided on composition, toxicity and adverse effects by means of an extensive search of the literature for the plants considered.

The WG activities in 2020 were two-fold:

- Validation of the composition/toxicity information retrieved for around 200 plant species, and coding of the relevant information so that it is ready to be transferred to the EFSA database;
- Development of the methodology to characterise the toxicity of the plant-based substances identified as of possible concern for human health. A combination of literature search, QSAR and read-across will be used for this purpose.

To fulfil the above objectives, in the course of 2020, 16 meetings were held for the review of the plants; additionally, 2 meetings were carried out on plant substances toxicity characterisation. Please refer to Annex 1 for further details on meeting dates and experts participation.

Due to Covid-19 pandemics, all meetings took place in the form of webconferences.

4. Next meeting(s)

As the project will continue over next three years, another series of meetings (19 for the validation of the remaining 700 plant species, and 4 for the plant substances toxicity characterisation) will be organised in 2021 with the same format.

A mid-term of the project meeting will be organised in September 2021 with the whole working group and the Contractor of the project to review progress made and agree on the working strategy for the second half of the project.

Annex I

22-Jun-20	22-Jun-20	Plant validation with Vittorio Silano
30-Jun-20	30-Jun-20	Plant validation with Massimo Collino
01-Jul-20	01-Jul-20	Plant validation with Qasim Chaudhry
06-Jul-20	06-Jul-20	Plant validation with Carlo Bicchi
07-Jul-20	07-Jul-20	Plant validation with Wirginia Kukula-Koch
16-Jul-20	16-Jul-20	Plant validation with Ulla Beckman-Sundh
17-Jul-20	17-Jul-20	Plant validation with Mauro Serafini
21-Sep-20	21-Sep-20	Plant validation with Robert Anton
08-Oct-20	08-Oct-20	Plant validation with Robert Anton
22-Oct-20	22-Oct-20	Plant validation with Vittorio Silano
13-Nov-20	13-Nov-20	Plant substances toxicity characterisation with Qasim Chaudhry
19-Nov-20	19-Nov-20	Plant validation with Carlo Bicchi
26-Nov-20	26-Nov-20	Plant validation with Vittorio Silano
30-Nov-20	30-Nov-20	Plant validation with Virginia Kukula-Koch
01-Dec-20	01-Dec-20	Plant validation with Mauro Serafini
09-Dec-20	10-Dec-20	Plant validation with Massimo Collino
17-Dec-20	17-Dec-20	Plant substances toxicity characterisation with Qasim Chaudhry
21-Dec-20	21-Dec-20	Plant validation with Carlo Bicchi



SCIENTIFIC COMMITTEE AND EMERGING RISKS UNIT

SCIENTIFIC COMMITTEE

MINUTES OF THE 28TH MEETING OF THE WORKING GROUP ON COMPENDIUM OF BOTANICALS

Held on 11 & 12 November 2019, Parma

(Agreed on 6 December 2019)

Participants

■ Working Group Members:

Robert Anton, Ulla Beckman-Sundh, Carlo Bicchi, Qasim Chaudhry, Massimo Collino, Mauro Serafini and Vittorio Silano (Chair).

■ External Contractors:

ECOMOLE: Krystof Dibusz, Pavla Vejvodova¹

Mario Negri Institute for Pharmacological Research: Emilio Benfenati²

■ EFSA:

SCER Unit: Bernard Bottex, Jean Lou Dorne

NUTRI Unit: Eirini Kouloura

■ Others:

EUROPOL: João Simões³

¹ Via webconference

² Participated to the discussion of agenda point 4.4 via webconference

³ Participated to the discussion of agenda point 4.3 via webconference

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Secundino Lopez Puente and Kirsten Pilegaard.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of Interest of Working Groups members

In accordance with EFSA's Policy on Independence⁴ and the Decision of the Executive Director on Competing Interest Management⁵, EFSA screened the Annual Declarations of Interest filled out by the Working Group members invited to the present meeting. No Conflicts of Interest related to the issues discussed in this meeting have been identified during the screening process, and no interests were declared orally by the members at the beginning of this meeting.

4. Scientific topic(s) for discussion

4.1. Transformation and further development of the EFSA Compendium of Botanicals (COMBO) (OC/EFSA/SCER/2015/05)

The working group reviewed the final report prepared by EcoMole for the COMBO Project that will end in December 2019. The report describes the activities performed these last four years to transform the initial Excel file into a web-accessible user friendly database, increase the number of plants in the Compendium and improve the quality of the information provided on composition, toxicity and adverse effects for around 1700 plant species.

The working group made a number of comments and suggestions to improve the content of the report. Suggestion was also made to publish a short fact sheet, together with this report, and the database summary reports, explaining in a couple of pages what the compendium is about and its purpose, what was done since the last version, and what will be the next steps.

The new version of the Compendium of Botanicals will be published together with the final report of the project and the above-mentioned fact sheet early 2020.

4.2. Assistance to the EFSA Emerging Risks Exchange Network (EREN)

Two briefing notes on possible emerging risks prepared by members of EREN were brought to the attention of the working group for possible review and comments.

The first issue concerns the use of ecdysteroids and more specifically ecdysterone in food supplements for anabolic purposes. The second issue is about the risk for hepatotoxicity associated with the consumption of turmeric or curcumin containing food supplements. The views of the working group were forwarded to the Secretariat of the network who will present them at the next meeting of the network.

⁴ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

⁵ http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/competing_interest_management_17.pdf

4.3. Assistance to EUROPOL

The working group was contacted by the European Counter Terrorism Centre of EUROPOL to review a draft report entitled "Poison Wars – Plant toxins; potential threats". This report was prepared in response to a series of publications from a group of terrorists explaining how to use 11 plant species to kill people. The Europol report is intended to raise awareness among law enforcement agencies on this possible threat.

The working group reviewed the draft report, making some suggestions to improve its usefulness. The Compendium of botanicals was used to retrieve additional LD50 values for the plants / substances of concern considered.

4.4. Consolidation and further development of the EFSA Compendium of Botanicals (COMBO2) (OC/EFSA/SCER/2018/03)

Following the activity described in section 4.1 of these minutes, EFSA identified the need i) to apply to an additional 900 plant species the same methodology applied to the above-mentioned 1700 plants to collect the scientific literature and retrieve relevant information on composition and toxicity/adverse effect, and ii) to characterise the toxicity of around 2500 substances flagged as of possible concern for human health in the first part of the project (COMBO).

For i), the working group recommended to follow the same approach used to retrieve relevant information for the 1700 plant species in order to avoid methodological discrepancies among the 2600 plant species that the database will contain at the end of the project.

Regarding ii), the working group acknowledged that for the majority of the substances flagged as of possible concern for human health, there will be little if no information available on toxicity in the literature. Decision was therefore made to use in silico methods + read across when experimental data are missing. Before doing so, the validity of the available in silico models will be tested with the substances flagged as of possible concern for human health that are already existing in the EFSA OpenFoodTox database, i.e. for which experimental data exist; the working group decided to consider the endpoint genotoxicity/mutagenicity for the testing phase.

4.5. Assistance to the EFSA NUTRI Unit

The working group was provided with an overview of the assistance provided to the EFSA NUTRI Unit with regard to the assessment of the notifications for traditional foods; the information contained in the Compendium of Botanicals and the expertise of the working group are used to complement the data provided in the notification. Two members of the working group were invited to volunteer to extract the relevant information for the assessment of *Plukenetia volubilis* roasted seeds as a traditional food.

Eirini Kouloura presented the new platform, called "Ratings", developed for the NUTRI Unit to collect and rate the literature retrieved for a given novel or traditional food.

5. Next steps

The working group was informed about the following activities for the beginning of 2020:

- Start validating the composition/toxicity information retrieved for the 900 plant species
- Draft the fact sheet on the Compendium of Botanicals to be published together with the final report of the COMBO project and the release of the updated database
- List the endpoints of interest for the characterisation of the toxicity of the substances of possible concern for human health and organise them by order of priority. For each endpoint, a description of the type of data/evidence needed will be provided in order to facilitate the search of the literature by the contractor.

The contractor will generate a list of the substances of possible concern that are already existing in OpenFoodTox. This list will be used for the testing of the available in silico models for prediction of toxicity.