

26 March 2024

09:30 – 17:00

MINUTES – Agreed on 12 Apr 2024

Location: Online

Attendees:

Working Group Members:

Antonio Hernández-Jerez, Laurentius (Ron) Hoogenboom, Hendrik van Loveren, Harry Mcardle, Susanne Hougaard Bennekou

EFSA:

MESE: Lucian FARCAL (Chair), Georgia BOMPOLA, Sara LEVORATO

NIF: Silvia VALTUENA MARTINEZ

FEEDCO: Chantra ESKES

Hearing expert:

US FDA: William B. Mattes¹

I. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Tanja Schwerdtle.

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. Agreement of the minutes of the 4th Working Group meeting held on 26th February 2024, via web-conference

¹ For Agenda item 6.2

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



The minutes of the 3rd Working Group meeting were agreed by written procedure on 8 March 2024.

V. Collaboration and engagement activities

5.1 Reporting from other relevant activities or meetings

The WG was informed on the presentation given by the WG coordinator at the 146th Plenary meeting of the NDA Panel (29 Feb 2024) followed by discussion with the panel members around the concepts included in the report, as well as on the future plans and relevancy for the assessments performed by the NDA Panel. Within this context, examples of biomarkers of effect used in previous assessments done by NDA Panel were already included in the working documents to support the discussions of the WG (see Item 6.1).

Finally, the colleagues that participated in the "International Symposium: Risk Assessment of Genotoxic Compounds – Challenges and Future Perspectives" (26-28 Feb 2024) reported also on this relevant event.

5.2 Dissemination plan

The WG was informed on other dissemination activities, in addition to those reported above. For the ongoing survey, a reminder was sent recently to stakeholders (the survey will be closed on 30 Apr 2024). A poster abstract was submitted to ESTIV Congress (3-6 Jun 2024), in addition to the oral presentation already accepted.

The project will be presented also at the next PPR Panel (18 April 2024), as part of the interactions and information exchange between the WG and the scientific Panels.

The WG was informed on the stakeholder workshop to be organised on 24-25 Jun 2024 and the proposed agenda, objectives and expected outcomes were discussed. More details will be shared with the WG members in order to contribute to the program.

VI. Scientific and technical topics

6.1 Feasibility study (Scientific Report)

Within this agenda item, the WG members further elaborated on the scientific report, with the aim to prepare a version of the document to be shared and presented at the next plenary meeting of the Scientific Committee (10-11 Apr 2024). The discussions addressed: 1) the title of the report, 2) the sub-types of biomarkers and their grouping based on the area of application, 3) the application of biomarkers, 4) definitions, with a focus on clarifications related to early versus late biomarkers of effect, the link to the AOPs and the KER quantitative understanding, described in the AOP framework, and 5) characteristics of biomarkers of effect. In addition, the description of biomarkers of effects (examples related to novel foods area) were discussed and refined by the WG members.



6.2 Food and Biomarkers: Finding the Right Recipe

This session was dedicated to a presentation given by William B. Mattes (invited as Hearing Expert) and discussion on the ongoing activities of the WG on biomarkers at US FDA, especially related to food safety. These included aspects related to biomarkers' definitions, characteristics of "ideal" biomarkers, different models or criteria used for their characterisation, translational biomarkers, AOPs, biological processes, adaptative processes. The outcome of the discussion will be further used by the WG at EFSA in the context of the Scientific Report development and beyond.

VII. Any Other Business

7.1 Next steps and actions

The WG compiled a list of actions for the next period. The focus will be on preparing a version of the Report to be discussed with the Scientific Committee, addressing the feedback received at the next plenary meeting and refining the report based on the existing comments in the document and previous discussions.

VIII. Next meeting

The next meeting will be held online on **26 April 2024**.

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26 February 2024

13:00 – 17:00

MINUTES – Agreed on 8 March 2024

Location: Telemeeting

Attendees:

Working Group Members:

Antonio Hernández-Jerez, Laurentius (Ron) Hoogenboom, Hendrik van Loveren, Harry Mcardle, Susanne Hougaard Bennekou

EFSA:

MESE: Lucian FARCAL (Chair), Georgia BOMPOLA, Sara LEVORATO, Alicia PAINI

NIF: Silvia VALTUENA MARTINEZ

FEEDCO: Anna CHRISTODOULIDOU, Chantra ESKEs, Paola MANINI

I. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Tanja Schwerdtle.

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 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. Agreement of the minutes of the 3rd Working Group meeting held on 24th January 2024, via web-conference

The minutes of the 3rd Working Group meeting were agreed by written procedure on 9 February 2024.

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. Collaboration and engagement activities

The WG was briefed on the presentation given by the WG coordinator at the 117th Scientific Committee plenary meeting on 5th Feb 2024 and feedback received. On that occasion, the SC was provided with an update on the ongoing activities of the biomarkers of effect project, underlying the main goal of the 1st phase of the project implemented as a descriptive approach that will create the base for the future guidance. The suggestions and comments received from the SC were summarised, as well as the actions taken (e.g. clarifications on terminology, elaborate on the main characteristics of biomarkers, challenges).

The WG was informed that a draft version of the report will be presented and discussed at the next SC plenary meeting on 10-11 April 2024.

In addition, the WG members were informed on the survey status and the dissemination plan.

VI. Scientific and technical topics

6.1 Description of biomarkers of effect

The WG initiated the discussion from a set of characteristics of 'ideal biomarkers' described in case of clinical use. The extrapolation of these characteristics to the risk assessment was then addressed in detail. First the grouping in analytical and biological characteristics was agreed, that correspond also to the aspects included within the validity evaluation of biomarkers.

The discussion was then focused on the biological characteristics, such as the predictivity, sensitivity and specificity, including their definitions and other clarifications regarding their importance in this context. Other aspects discussed refer to the biological plausibility, irreversibility and the 'point-of-no-return', quantifiability, magnitude of change versus normal variability, human relevance, etc.

Further, the template developed for the biomarker's description (including representative examples extracted from published Scientific Opinions of EFSA) was discussed and refined. The current version of the template includes five groups of descriptors: general identification, adverse outcome description, link to existing AOPs, risk assessment descriptors and references.

VII. Any Other Business

7.1 Next steps and actions

The WG compiled a list of actions for the next period, aiming to achieve a version of the report ready for discussion with the SC at the next plenary meeting (10-11 April 2024).

The focus of the WG members in next period will be on refining the sections of definitions and description (characteristics) of biomarkers of effect.



VIII. Next meeting

The next meeting will be held online on **26 March 2024**.

Location: Online

Attendees:

Working Group Members:

Antonio Hernández-Jerez, Laurentius (Ron) Hoogenboom, Hendrik van Loveren, Harry Mcardle, Tanja Schwerdtle

Hearing experts:

Robert Pasanen-Kase¹

EFSA:

MESE: Lucian FARCAL (Chair), Georgia BOMPOLA, Sara LEVORATO, Alicia PAINI

FIP: Cristina CROERA

NIF: Silvia VALTUENA MARTINEZ

FEEDCO: Anna CHRISTODOULIDOU, Chantra ESKEs

I. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Susanne Hougaard Bennekou.

II. Adoption of agenda

The agenda was adopted with small changes in the timing of the sessions.

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. Agreement of the minutes of the 2nd Working Group meeting held on 17 November 2023, via web-conference

¹ For Agenda Item 6.1

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



The minutes of the 2nd Working Group meeting were agreed by written procedure on 5 December 2023.

V. Collaboration and engagement activities

The WG members were informed on the Survey "[Mapping of initiatives, expertise and knowledge around biomarkers of effect](#)" launched in January 2024. The aim of the survey is to create awareness regarding EFSA's initiative and to collect input from stakeholders in its initial phase and that could support further the project development. The survey will be closed on 30 April 2024 and the results will be used for the development of the Scientific Report by the WG members. The survey has been distributed to different EU and international organisations. In addition, the WG members suggested few other organisations that could be contacted, as relevant for this topic. It was also proposed to distribute the survey to EFSA Panels, for information.

5.1 Reporting from other relevant activities or meetings

The WG members were informed regarding several dissemination activities (e.g. presentations at EFSA Scientific Committee and Panels meetings, bilateral meeting with members of PARC), aiming at complementing the collaboration and engagement plan towards the development of the guidance within an international platform/mechanism.

VI. Scientific and technical topics

6.1 OECD Occupational Exposure and Effect Biomonitoring Activities - Discussion of Knowledge Exchange and Synergies with EFSA Effect-Biomarker WG

Hearing Expert (Robert Pasanen-Kase) presented the OECD project on Occupational Exposure and Effect Biomonitoring activities and facilitated the discussions of knowledge exchange and synergies with EFSA WG Biomarkers of effect. OECD project pursues synergies with relevant initiatives on biomarkers (e.g. PARC, EFSA) aiming at the reduction of work duplication and the harmonisation of terminologies and methodologies.

The presentation included aspects related to Occupational Biomonitoring, its challenges and the role of effect-biomarkers in this context, characterisation of biomarkers and the link to the Adverse Outcome Pathways (AOPs) approach. Finally, the case studies included in this project have been briefly described, including the plans for the publication of the project outcomes (e.g. guiding principles).

The discussion with the WG referred to the effect-biomarkers relevance, their interpretation in the risk assessment context, case studies, physiological versus adverse effects and similarities with other risk assessment areas. It was generally agreed that the outcomes from the OECD project represent relevant resources for the WG, to be further reviewed and used by the WG members.



6.2 Deliverable 1 - Feasibility study

In this session, the working draft of the Scientific Report was discussed. Several sections were therefore refined, focusing particularly on the Introduction, Scope and Definitions sections. Members of the WG made additional remarks on the schematic depiction of the scope and its further refinement e.g. including the visualisation of up- and down-stream biomarkers in relation to the critical effect/adverse outcome. As clarifications on terminologies is an important part of the mandate, the WG further discussed on the way forward regarding the terms related to biomarkers of effect used in different contexts.

Further, a new background text on the definitions, classification and application of biomarkers was discussed and reviewed by the WG members and it will be further integrated in the core report.

Part of this session was dedicated to the current format to describe the biomarkers of effect in parallel with several examples extracted from published EFSA Scientific Opinions. As a next step, WG members will complete the description, while the next WG meeting will be dedicated exclusively to the topic.

6.3 Deliverable 2 - Mapping study

The status of the inventory of resources was presented to the WG. Part of this activity will be outsourced starting from 1st Feb 2024 aiming to support the WG with the identification and reviewing of additional resources related to this topic. The outcome will be part of the Scientific Report.

VII. Any Other Business

7.1 Next steps and actions

The WG compiled a list of actions for the next period, with the aim of achieving a draft report ready for discussion by the Scientific Committee in Q2 2024. In addition, several actions regarding the dissemination activities, were added, including further distribution of the survey discussed above.

VIII. Next meeting

The next meeting will be held online on **26 February 2024**.

17 November 2023

09:30 - 17:00

MINUTES - Agreed on 6 December 2023

Location: Online

Attendees:

Working Group Members:

Susanne Hougaard Bennekou, Laurentius (Ron) Hoogenboom, Hendrik van Loveren, Harry Mcardle, Antonio Hernández-Jerez.

EFSA:

MESE: Lucian FARCAL (Chair), Georgia BOMPOLA, Sara LEVORATO

FIP: Cristina CROERA, Zainab AL HARRAQ

NIF: Agnès DE SESMAISONS

FEEDCO: Anna CHRISTODOULIDOU, Chantra ESKEs, Paola MANINI

I. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Tanja Schwerdtle.

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. Agreement of the minutes of the 1st Working Group meeting held on 25 October 2025, via web-conference

The minutes of the 1st Working Group meeting were agreed by written procedure on 23 November 2023.

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. Scientific topics for discussion

5.1 Deliverable 2 - Mapping study

The progress related to Deliverable 2 (mapping study) was presented to the WG. This is developed to fulfill Objective 2 of the project referring to reviewing and mapping the activities, initiatives, knowledge, approaches relevant to the project goal. The outcome will be included as Annex to the Scientific Report resulting from this project. As a first step, the structure of the inventory was created and completed with several resources (relevant projects, databases and publications). The WG discussed further the development of the inventory, information to be included and its use in the context of the feasibility study. As a next step, it was agreed to enhance some of its functionalities, e.g. for tracking new resources added and to include more resources. The project plan for 2024 includes that part of this task will be outsourced.

5.2 Deliverable 1 - Feasibility study

In this session, the WG members were updated regarding the structure of the report (agreed during the 1st meeting) and the status for each section. The focus is currently on developing the introduction (including the scope of the study), definitions, description of biomarkers of effect along with representative examples to support this work. These were further discussed in detail in the next agenda items (5.2 to 5.6).

5.3 Deliverable 1 - Introduction and scope

The WG discussed on the Scope section and the comments received on the initial text. In addition, the WG members worked on a figure that could be used to visualise the elements that are included/excluded from the scope of the study. More specifically, the WG discussed and acknowledged the complexity of addressing together the biomarkers of beneficial and adverse effects, therefore it was proposed that only safety assessment aspects and biomarkers of (adverse) effects should be included within the scope. Aspects related to the beneficial effects / food health claims will be covered and explained in the introduction section. Further, in order to capture all relevant aspects, the WG will create a list of issues that could be considered in the current report or addressed in the next phase of the project.

5.4 Deliverable 1 - Definitions of biomarkers of effect

The WG discussed around an initial proposal regarding definitions, the existing reports referring to biomarkers of effect and related terms considered in the report. The WG looked comparatively at definitions used in previous reports, guidance documents or publications. As a next step, the WG will agree on a general definition for biomarkers of effect to be used. In addition, it will be necessary to work and clarify on other terms (e.g. intermediate events, intermediate and apical endpoints) that are used in this context and compile them in a



glossary. The link with other concepts (e.g. biomarkers of exposure, biomarkers of susceptibility, adverse outcome pathways) will be also considered.

5.5 Deliverable 1 - Examples of biomarkers of effect

The WG discussed around an initial list of examples of biomarkers of effects, used to derive Reference Points for different chemicals and extracted from EFSA's Scientific Opinions. The list includes, for example, biomarkers of effect used for in the assessments of bisphenol A, per- and polyfluoroalkyl substances (PFAS), copper, etc. The WG will work on extending the list and extract useful aspects for the identification and characterisation of biomarkers of effect (see Agenda item 5.6).

5.6 Deliverable 1 - Description of biomarkers of effect

Following the previous discussion (Agenda item 5.5) regarding biomarkers of effect used in a regulatory risk assessment context, the WG agreed to compile a list of key descriptors and aspects for their identification and characterisation. The list will be further refined and harmonised to be useful for the next steps of the project. For each descriptor, the main elements to be reported will be detailed and create the basis for further methodology and guidance development.

VI. Any Other Business

6.1 Collaboration and engagement activities

The WG was informed on the collaboration and engagement plan and ongoing actions. As a short/medium-term activity, a stakeholders' survey is in preparation, with the plan to be launched in Q1 2024. This should create awareness on EFSA's initiative, support the collection of input on existing initiatives, expertise and other scientific aspects. Overall, it should complete the feasibility study and help in identifying the mechanism for co-creation of the guidance (in Phase 2 of the project) within an international partnership. The WG will be consulted further regarding the content of the survey.

6.2 Next steps and actions

A list of immediate actions was compiled and discussed. The focus in the next period will be on clarifications regarding the scope of the self-task mandate, definitions and description, starting from the examples of biomarkers of effect used in a regulatory risk assessment context.

VII. Next meeting

The next meeting will be held online on 24 January 2024.

Location: Online

Attendees:

Working Group Members:

Susanne Hougaard Bennekou, Laurentius (Ron) Hoogenboom, Hendrik van Loveren, Harry Mcardle, Tanja Schwerdtle.

EFSA:

MESE: Lucian FARCAL (Chair), Georgia BOMPOLA, Sara LEVORATO

FIP: Cristina CROERA, Zainab AL HARRAQ

NIF: Silvia VALTUENA MARTINEZ

FEEDCO: Anna CHRISTODOULIDOU, Paola MANINI

I. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Antonio Hernández-Jerez.

Tanja Schwerdtle attended half of the meeting (agenda items 1 to 5.4).

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. Tour de table

The participants in the meeting introduced themselves, their expertise and other relevant activities especially related to EFSA's Panels, WGs or Units.

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. Scientific topics for discussion

5.1 Terms of reference and project plan

The Scientific Committee requested and received from EFSA the mandate related to the “Guidance on the use of biomarkers of effect in regulatory risk assessment of chemicals” (EFSA-Q-2023-00583³). This project will be implemented in two phases: feasibility study (phase 1) and guidance development (phase 2), with the overall goal to work towards guidance on the use of biomarkers of effect to derive Reference Points (RPs) for establishing Health Based Guidance Values (HBGV) or deriving Margins of Exposure (MoE).

The project plan and timelines were presented by the Chair, with a focus on the feasibility study to be performed in the first twelve months of the project. This includes activities related to definitions and description of biomarkers of effect and the overall scope of the guidance. These tasks will be completed by a mapping study, that will compile and review initiatives, approaches and publications relevant to the project. The outcome of phase 1 will include conclusions and recommendations from the WG regarding the feasibility of such guidance.

5.2 Collaboration and engagement activities

The aim of the project is to achieve an internationally agreed guidance by establishing consultation and co-creation mechanisms within EU (e.g. Member States, EU Agencies, European Commission), international (e.g. OECD, WHO) and other national organisations (e.g. US FDA, Health Canada). For this, the feasibility study should identify and recommend a way forward in developing the guidance, jointly with other organisations.

These mechanisms could include consultations on the main outcomes, endorsement of the approaches proposed and/or direct involvement in the process (co-creation). The involvement of relevant organisations from the initial phases of the project is essential for achieving an internationally agreed guidance at a later stage. A collaboration and engagement plan is being developed by EFSA and the WG will be consulted further on these activities.

5.3 Deliverable 1 Report

Within this Agenda item, the plan for Phase 1 and its main outcome was presented by the meeting Chair. The WG will work on a Scientific Report (Deliverable 1 of the project) to be published in EFSA Journal (Q3 2024) and to be used as a base for further development of guidance. The report will define the scope and limitations of the approach, will address several challenges especially related to the definitions of biomarkers of effect and other relevant terms, descriptors for their identification and characterisation and any other scientific concepts needed in this context.

³ <https://open.efsa.europa.eu/questions/EFSA-Q-2023-00583>



The work will also include the identification and analysis of representative examples of biomarkers of effect that have been used already by EFSA's Scientific Panels to derive Reference Points and use them along the project implementation. The examples will be included as an Annex to the scientific report.

5.4 General discussion on the project plan and Deliverable 1

Several aspects and challenges were discussed by the WG members, e.g. *i*) clarifications regarding the scope, applicability and limitations of the concepts to be developed, *ii*) a general and broader scope of the project, that would cover the adverse effects, as well as the beneficial effects (addressing toxic substances and also nutrients), versus a more focused scope, *iii*) use of existing examples from EFSA's Scientific Opinions, especially for the definition and description of biomarkers of effect.

The WG discussed on the main challenges, possible solutions and their prioritisation (starting from a previously prepared draft list). It was concluded that Phase 1 should provide a set of recommendations for the further development of the guidance and solutions to the identified challenges.

5.5 Definitions related to biomarkers of effect

The discussion within the WG started from the existing definitions of biomarkers of effect and related terms that should be clarified and used first (e.g. available definitions and concepts developed by other organisations (e.g. WHO, OECD, FDA) and investigate which elements should be used as such or adapted.

As harmonisation of terms is needed, the WG should discuss regarding the link between "biomarker of effect" and related terms that are often used interchangeably (e.g. intermediate events, effects and endpoints, surrogate endpoints, markers of status).

5.6 Description of biomarkers of effect

The WG members discussed the options for the description of biomarkers of effect that could include different type of descriptors, e.g. for the identification, characterisation, classification or measurements of biomarkers of effects. It was discussed that the description should include different aspects, e.g. naming and other identifiers, relevant biological process or level of organisation, measurement methods and matrixes, other mechanistic information.

5.7 Other scientific concepts

The WG considered that the work on the definition and description of biomarkers of effect may also bring clarifications regarding other aspects, e.g. whether the effect in question constitutes an impairment, a disease or rather a change in homeostasis, the specificity of the biomarkers of effect, the predictive power of the biomarkers of effect (e.g. sensitivity and the



magnitude of the response to the stimulus, the correlation of a decrease/increase of a biomarker with the adverse effect), their human/animal relevance, the use of *in vitro* measurements and creation of batteries of biomarkers of effect/multimodal biomarkers, especially in the context of a transitioning towards new approach methodologies (NAMs) to enhance their predictivity in risk assessment, the link to the adverse outcome pathways (AOPs) approach.

VI. Any Other Business

6.1 Distribution of tasks, responsibilities and expectations

Following the presentation of the project plan, the outline of deliverable 1 and discussion, different tasks towards developing the report were distributed to WG members. The first steps will include working on the scope of the report, the definitions of biomarkers of effects and extraction of representative examples of biomarkers of effect from EFSA's Scientific Opinions.

VII. Next meeting

The next meeting will be held online on **17 November 2023**.
