Scientific Panel on GMO

Minutes of the 118th Plenary meeting of the Scientific Panel on GMO

25-26 October 2017, Parma

(Agreed on 28 November 2017)

Participants

- **Panel members**:

Josep Casacuberta, Adinda De Schrijver, Mikolaj Antoni Gralak, Philippe Guerche, Huw Jones, Barbara Manachini, Antoine Messéan, Hanspeter Naegeli, Elsa Nielsen, Fabien Nogué, Christophe Robaglia, Nils Rostoks, Jeremy Sweet, Francesco Visioli and Jean-Michel Wal.

- **European Commission representatives:** Lisa Haller, Béatrice Marquez-Garrido (web), and Hans Moons (DG SANTE).

- **EFSA:**

GMO Unit: Fernando Álvarez, Michele Ardizzone, Herman Broll, Giacomo De Sanctis, Yann Devos, Antonio Fernández Dumont, Andrea Gennaro, José Ángel Gomez Ruiz, Mildred Hauck, Anna Lanzoni, Sylvie Mestdagh, Irina Olaru, Nikoletta Papadopoulou, Claudia Paoletti, Konstantinos Paraskevopoulos, Matthew Ramon and Elisabeth Waigmann.

Other EFSA Units/Directorates: none.

- **Observers (in application of the guidelines for observers)**:
    - **Attending physically in Parma:** Pascale Delzenne (Monsanto), Zsolt Jekkel (Pioneer Hi-Bred), Maria Koster (COGEM), Petra Kostolaniova (EuropaBio), Federica Manini (Soremartec Italia SRL), Maica Martinez Parrilla (Bayer), Nancy Podevin (DuPont Pioneer), Lisette van der Knaap (COGEM)
    - **Attending via web streaming:** Oksana Apanasets (Bayer), Bence Balogh (Bayer Hungária Kft.), Elena Cogalniceanu (EAS Strategies), Tewodros Duressa (Monsanto Europe), Juliane Geike (KWS SAAT SE), Gijs A. Kleter (RIKILT Wageningen University & Research), Debora Leite (Vigna Brasil), Alexandra Lensch (Evonik Nutrition & Care GmbH), Anja Matzk (KWS SAAT SE), Sara Nigro (Syngenta), Romaan Raemaekers (Syngenta), Sever Rotaru (Canadian Food Inspection Agency), Sabine Storck-Weyhermueller (Syngenta), Kate Trollope (EU Food Policy), Christine Wandelt (BASF Plant Science Company GmbH), Irina Wenderoth (BASF Plant Science)
- **Others:** none.

1 Welcome and apologies for absence

The Chair of the EFSA GMO Panel welcomed the participants. Apologies were received from Nicholas Birch and Christoph Tebbe.

Philippe Guerche did not participate in agenda point 7.3 due to a Conflict of Interest being identified for the agenda item.

2 Brief introduction of Panel members and Observers

The Chair welcomed the participants and invited them to introduce themselves.

3 Adoption of agenda

The agenda was adopted with the following changes: points 8.3.1, 8.3.2, 9.1.2, 9.2.3, and 12.1 were added.

4 Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[1] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[2], EFSA screened the Annual Declarations of Interest (ADoIs) and the Specific Declarations of Interest (SDoIs) filled in by the experts invited to the present meeting. For further details on the outcome of the screening of the ADoI and SDoI, please refer to Annex I. Oral Declaration of Interest was asked at the beginning of the meeting and no additional interest was declared.

5 Presentation of the Guidelines for Observers

A member of the GMO Unit presented the EFSA Guidelines for Observers attending open plenary meetings.

6 Report on written adoption procedure since 117th Plenary meeting

The minutes of the 117th Plenary meeting held on 20-21 September 2017 were adopted by written procedure on 27 September and were published on 4 October on the EFSA website at: Event: 117th plenary meeting of GMO Panel.

7 Scientific outputs submitted for discussion and/or possible adoption

7.1 Assessment of genetically modified oilseed rape MS8, RF3, and MS8 × RF3, for renewal of the authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO-RX-004) (EFSA-Q-2016-00569)

This was the first time the GMO Panel discussed the draft opinion.

Oilseed rape MS8 and RF3 produce the Barnase and Bastar proteins, which control pollen formation, and the PAT protein, which confers tolerance to glufosinate. These events and the two-event stack had been assessed by the GMO Panel in the context of application C/BE/96/01[3] and were authorised by Commission Decision 2007/232/EC; application

[1] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[2] http://www.efsa.europa.eu/sites/default/files/assets/independencerules2014.pdf
[3] http://www.efsa.europa.eu/en/efsajournal/pub/28

EFSA-GMO-RX-004 was submitted to EFSA in the context of the renewal of the authorisation.

The GMO Panel adopted this scientific opinion, which will be published in the EFSA Journal.

The Chair invited observers to ask questions on this agenda item. An observer asked how the scope of the application as indicated in the mandate from EC will be reflected in the scientific opinion, to which EFSA replied that this issue will be discussed with EC and the opinion will reflect the outcome.

7.2 Assessment of genetically modified sugar beet H7-1 for renewal of authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO-RX-006) (EFSA-Q-2017-00026)

This was the first time the GMO Panel discussed the draft opinion.

Sugar beet H7-1 produces CP4 EPSPS, which confers tolerance to glyphosate. This event has been assessed by the GMO Panel in the context of application EFSA-GMO-UK-2004-08[4] and was authorised by Commission Decision 2007/692/EC; application EFSA-GMO-RX-006 was submitted to EFSA in the context of the renewal of the authorisation.

The GMO Panel adopted this scientific opinion, which will be published in the EFSA Journal.

The Chair invited observers to ask questions on this agenda item, but there were no questions.

7.3 Assessment of genetically modified soybean MON 87751 for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2014-121) (EFSA-Q-2014-00719)

This was the first time the GMO Panel discussed the draft opinion.

Soybean MON 87751 was developed to produce two new proteins, Cry2Ab2 and Cry1A.105, which confer resistance against certain lepidopteran pests.

The GMO Panel discussed the draft scientific opinion, specifically the sections on molecular characterisation, comparative analysis, food/feed safety assessment and environmental risk assessment. Further discussion is needed.

The Chair invited observers to ask questions on this agenda item. An observer asked whether data submitted under Article 6 of Regulation (EU) No 503/2013 will be reported separately in scientific opinions. EFSA replied that all data of relevant studies is assessed with the same degree of scientific rigour, independently on it being legally required, requested by EFSA and the GMO Panel, or submitted spontaneously by applicants. Relevant studies will be reported under the appropriate section in the opinion.

7.4 Assessment of genetically modified maize MON 87427 × MON 89034 × MIR162 × NK603 and subcombinations, for food and feed uses, under Regulation (EC) No 1829/2003 (application EFSA-GMO-NL-2015-131) (EFSA-Q-2016-00148)

The GMO Panel had first discussed certain sections of this draft scientific opinion in its previous plenary meeting.[5] In this meeting, the GMO Panel discussed the sections on molecular characterisation, comparative assessment, food/feed safety assessment and environmental risk assessment. Further discussion is needed.

The Chair invited observers to ask questions on this agenda item. An observer asked whether the requirement for 90-day studies for each event will be maintained also for

[4] http://www.efsa.europa.eu/en/efsajournal/pub/431
[5] http://www.efsa.europa.eu/sites/default/files/event/170920-m.pdf

stacked events, to which the representative of the European Commission replied that the requirement is applicable for the single transformation events in stacks and additionally (when indications of potential adverse effects) for the stacked transformation events.

8 New mandates

8.1 Applications under Regulation (EC) No 1829/2003

None.

8.2 Annual PMEM reports

None.

8.3 Other Requests and Mandates

Two mandates have been received since last reported in the GMO Panel plenary meeting:

8.3.1. Mandate to assess additional information related to the application for authorisation of food and feed containing, consisting and produced from genetically modified maize Bt11 x 59122 x MIR604 x 1507 x GA21 and genetically modified maize combining two, three or four of the events under Regulation 1829/2003 (EFSA-Q-2017-00669)

8.3.2. Mandate to develop a technical note to the applicants on, and checking of, the quality of the methodology, analysis and reporting covering full sequencing and insertion site analysis of the genetically modified (GM) event, and generational stability and integrity (EFSA-Q-2017-00706)

9 Feedback from the Scientific Committee/ Scientific Panels, EFSA and the European Commission

9.1 Scientific Committee and/or Scientific Panel(s) including their Working Groups

9.1.1. Scientific Committee

The vice-Chair and the Chair of the GMO Panel reported on the 84th (12-13 July 2017) and 85th (13-14 September 2017) Scientific Committee plenary meetings respectively. Minutes of these meetings are available on the EFSA website.[6,7]

9.1.2. Feedback from ERA WG on PMEM reports

In the context of the assessment of several applications for the renewal authorisation of GM plants for food and feed uses, import and processing, the environmental risk assessment (ERA) working group has been analysing the content of the annual post market environmental monitoring (PMEM) reports as well as the relevance of their underlying monitoring methodology. The PMEM plans proposed by applicants consist mainly of general surveillance of imported GM plant material. This general surveillance is coordinated by EuropaBio and implemented by selected operators (federations involved in import and processing). In addition, applicants review relevant scientific publications retrieved from literature searches on an annual basis. Although the final adoption of the PMEM plans fall outside the remit of EFSA, the GMO Panel considers that further discussion with applicants and risk managers is needed on the practical implementation of the PMEM for GM plants for import and processing.

[6] https://www.efsa.europa.eu/sites/default/files/event/170712-m.pdf
[7] https://www.efsa.europa.eu/sites/default/files/event/170913-m_0.pdf

9.2 EFSA including its Working Groups/Task Forces

9.2.1 EFSA's 3rd Scientific Conference

A member of the GMO Unit presented the main themes of EFSA's 3rd Scientific Conference, which will be held in Parma, on 18-21 September 2018.

9.2.2 EFSA Colloquium on the use of omics in risk assessment

A member of the GMO Unit presented the main topics to be covered by a scientific colloquium on the use of omics in risk assessment, which will be held in Berlin, on 24-25 April 2018.

9.2.3 Panel renewal

A member of the GMO Unit presented the current status and next steps of the GMO Panel renewal process.

9.3 European Commission

The representatives of the European Commission informed the Panel on their on-going activities, approval procedures for applications for which the GMO Panel had issued a scientific opinion, and upcoming mandates.

10 Other scientific topics for information and/or discussion

10.1 Explanatory note on literature searching

A member of the GMO Unit presented the explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorisation and annual PMEM reports on GMOs authorised in the EU market.[8] This explanatory note to the guidance clarifies the scope and methodology for literature searching performed in the context of applications for market authorisation of GMOs submitted under Regulation (EC) No 1829/2003 before and after Regulation (EU) No 503/2013 entered into force, annual PMEM reports on GMOs authorised in the EU market, and applications for the renewed market authorisation of GM food/feed authorised under Regulation (EC) No 1829/2003. It also gives recommendations on how to conduct and report systematic/extensive literature searches, and to present the results of any scoping reviews. The explanatory note, its practical implementation and possible issues for revision were presented and discussed by the GMO Panel.

The Chair invited observers to ask questions on this agenda item. An observer asked about the usefulness of reference study searches. EFSA replied that applicants should use a subset of representative publications, if available, complying with the eligibility/inclusion criteria, in order to test, fine-tune and validate the search strategy as part of the protocol development (thus before conducting the actual search). This testing should enable applicants to check if the strategy suggested for the review is suitable to retrieve the already known literature on the topic. The retrieval of all reference publications within the results in the queried information sources suggests that the search strategy is performing at least adequately, and provides a means to validate the searches. It was also clarified that the testing of the search strategy is an iterative process and that there is added value in reporting the outcomes of these preliminary searches.

10.2 RNAi strategy document

A member of the GMO Unit presented the internal note on the strategy and technical aspects relevant for small RNA plant off-target bioinformatics studies. According to

[8] http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2017.EN-1207/epdf

Regulation (EU) No 503/2013, when silencing approaches by RNAi expression have been used in GM plant applications, a bioinformatic analysis to identify potential 'off target' genes is required. The GMO Panel's Molecular Characterisation Working Group and EFSA staff have discussed the issue extensively and prepared a strategy to deal with small RNA off-target bioinformatic analysis in plants. This is based on the current knowledge and may evolve with the progress of the knowledge in the field. The Panel discussed the document, which was endorsed (please see Annex II).

The Chair invited observers to ask questions on this agenda item, but there were no questions.

11 Answers to questions from Observers (in application of the EFSA Guidelines for Observers)

Observers were invited to submit questions for the GMO Panel Plenary meeting at the time of registration. These questions, the corresponding answers and other interventions related to them, are listed below:

1. "If we are now preparing data for a new application process, which guidance, especially for the description/characterization of microorganisms should we use? What would be your recommendation?"

EFSA replied that applications for products derived from genetically modified microorganisms are submitted under the sectoral legislation relevant for the product in question, provided that the product does not contain genetically modified DNA or microorganisms. Therefore, these products are not assessed by the GMO Panel, but by the panel dealing with the respective sectoral legislation. For example, feed additives derived from genetically modified microorganisms are assessed by the FEEDAP Panel. The FEEDAP Panel's draft guidance on the characterisation of microorganisms used as feed additives or as production organisms[9] was up for public consultation until 15 September; the GMO Panel was consulted on this guidance. Once adopted, this guidance is expected to have a grace period before it will enter into force. For the time being, the GMO Panel's 'Guidance on the risk assessment of genetically modified microorganisms and their products intended for food and feed use'[10] applies. Further support for submitting an application can be solicited from the EFSA Application Helpdesk, who handles applications for regulated products and who provides assistance to applicants, via the "Ask a question" section on the EFSA website.[11]

2. "Given the amount of data previously generated for GM stacks and the lack of adverse effects, could the Panel revisit the minimum data requirements case by case, based on the principles of the guidelines and legislation? If so, how this could be initiated for discussion?"

EFSA replied that the approach for the risk assessment of stacks is defined in Regulation (EU) No 503/2013, so GMO Panel does not have much flexibility to investigate possible changes to the approach. A representative of the European Commission added that there is no reason to deviate from legislation for this matter.

[9] http://www.efsa.europa.eu/en/consultations/call/170615
[10] http://www.efsa.europa.eu/en/efsajournal/pub/2193
[11] http://www.efsa.europa.eu/en/applicationshelpdesk/askaquestion

3. "Given the positive experience with the Focus group for the allergenicity guidance, will this group contribute to the assessment of any revisions to the in vitro protein digestibility?"

EFSA replied that The "Focus group" project was a positive experience aiming to engage with stakeholders and Member States and to enhance the quality, clarity and usability of the guidance document. In this context, EFSA would welcome the possibility of involving the "Focus group" consultative body in the revisions to the in vitro protein digestibility test. EFSA will further investigate what opportunities are available for the Focus group involvement in future work, considering availability of members, timelines, budget, An initial proposal is as follows: as described in the guidance document[12], EFSA developed principles for a refined in vitro protein digestion test and established an interim phase to confirm its applicability in the risk assessment context. To this end, EFSA launched a procurement call published on 26th of July 2017 that is currently ongoing and that will last for 20 months after the entry into force of the contract. After this period, EFSA will assess whether the refined test adds value to the allergenicity risk assessment and, if so, what further steps are needed for its final implementation in the form of guidance for applicants. At this stage, EFSA could actively involve the "Focus group". For the specifics, EFSA will present a proposal to the "Focus group" members at due time.

An observer wished to express the appreciation of EuropaBio members for the Focus group project.

4. "What will be the use of the external report 'Development and harmonisation of reliable sampling approaches for generation of data supporting GM plants risk assessment'?"

EFSA replied that the report has been produced by an external contractor, following a public tender procedure. EFSA launched this contract to further develop best scientific practice for data collection in risk assessment, to take into account the recent developments in the area of sampling for risk assessment. The report addressed 3 tasks: 1) provide an analysis of where sampling takes place in GMO risk assessment; 2) screen the scientifically recognised sampling standards, frameworks and guidelines currently used to generate data for GM plant risk assessment, and evaluate whether these strategies are sufficient to ensure that the data collected are representative; 3) define and develop sampling strategies that ensure the collection of representative data and proposes a comprehensive outline to reach this goal. The report highlights deficiencies in reporting of sampling protocols and highlights the need to eliminate bias-generating errors to secure sampling representativeness. It provides concrete suggestions to ensure that only representative sampling methods are used to provide the data necessary for GM plant risk assessment. The report also indicates that some methodological/ scientific assumptions made regarding sampling operations are not always reported in submitted applications. As no specific requirements for approaches to sampling have been yet laid down in EU legislation, EFSA has proactively commissioned this report to ensure consistency of sampling approaches across applications. The report

[12] EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli H,Birch AN, Casacuberta J, De Schrijver A, Gralak MA, Guerche P, Jones H, Manachini B, Messean A,Nielsen EE, Nogue F, Robaglia C, Rostoks N, Sweet J, Tebbe C, Visioli F, Wal J-M, Eigenmann P, Epstein M, Hoffmann-Sommergruber K, Koning F, Lovik M, Mills C, Moreno FJ, van Loveren H, Selb R and FernandezDumont A, 2017. Guidance on allergenicity assessment of genetically modified plants. EFSA Journal2017;15(5):4862, 49 pp. https://doi.org/10.2903/j.efsa.2017.4862

recommends that applications should provide information on sampling approaches in full; more broadly, it highlights how new developments in the area of data collection could be applied, and provides recommendations on how EFSA's risk assessment might incorporate the most relevant and the latest knowledge on sampling. EFSA may organize a meeting with industry - with the aim of collecting and discussing background information on the sampling procedures. The legislation allows for the RA process to be updated when new information and science becomes available. This makes the system responsive and rigorous. This report ensured that up-to-date knowledge is made available to EFSA to further improve its approach to risk assessment. The present report provides information that EFSA may use to further improve its guidance documents, as it offers a science-backed basis for checking appropriateness of sampling procedures.

5. "Following the cancellation of the webinar on next generation sequencing, could you provide an update on this topic?"

EFSA replied that to ensure continued verification as agreed with applicants and to harmonise further applicants' submission of data, the Commission has mandated EFSA to develop a single document which will put together all the requirements and recommendations for the use of DNA sequencing information for the sequencing of insert(s) and flanking regions, insertion site analysis and generational stability and integrity, in the context of the risk assessment of GMOs. This document will therefore start from the JRC guidelines related to sequencing of the insert(s) and flanking regions and improve these where scientifically justified. This will ensure continuity regarding the minimum requirements and recommendations for the sequencing of the insert(s) and flanking regions (currently checked by DG JRC). Additionally, the document will cover junction read analysis and generational stability and integrity when addressed by next generation sequencing.

An observer indicated that different applicants use different approaches for the molecular characterisation of GMOs and asked whether EFSA foresees a discussion with applicants on the diversity of techniques used. EFSA replied that it will investigate the possibilities for dialogue with applicants on this topic.

12 Any other business

12.1 Feedback on the open plenary

A member of the GMO Unit invited the observers to fill in the feedback form they would receive after the meeting.

Annex I

Interests and actions resulting from the screening of Annual Declarations of Interest (ADoI) or Specific Declarations of Interest (SDoI)

CONFLICT OF INTEREST: In the SDoI filled for the present meeting, Philippe Guerche declared an interest for Item 7.3 in relation to previously declared annual declaration of interest (ADOI): Mr Guerche commented on dossiers submitted to EFSA, including Application for authorisation of genetically modified soybean MON 87751 for food and feed uses, import and processing submitted to EFSA under Regulation (EC) No 1829/2003 by Monsanto (EFSA-GMO-NL-2014-121), in his capacity as member of the French High Council for Biotechnology (FSO), which advises the French government on GMOs. In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[13] and the Decision of the Executive Director on Declarations of Interest[14], and taking into account the specific matters discussed at the meeting in question, the interests above were deemed to represent a Conflict of Interest.

This results in the exclusion of the expert from any discussion, voting or other processing of the agenda item 7.3.

[13] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[14] http://www.efsa.europa.eu/en/keydocs/docs/independencerules2014

Annex II

Internal note on the strategy and technical aspects for small RNA plant off-target bioinformatics studies

According to the Regulation (EU) No 503/2013, when silencing approaches by RNAi expression have been used in GM plant applications, a bioinformatic analysis to identify potential 'off target' genes is required. The EFSA GMO panel acknowledges the limitations of bioinformatic searches for potential off-targets of siRNAs or artificial miRNAs produced by GM plants engineered to reduce the level of certain RNAs (Paces et al, EFSA supporting publication 2017; EFSA 2014, Casacuberta et al, 2015; Ramon et al, 2014; Lundgren et al, 2013). In plants a set of parameters allows for a reasonable prediction of RNAi off-target genes while in human and animals the extent of complementarity between the small RNA and the target is more limited and therefore these prediction tools do not allow for sufficiently reliable predictions (Pinzón et al, 2017). Therefore the GMO Panel considers that only the search for small RNA off-targets in the GM plant could have value for the risk assessment of GM plants.

As described in the literature review of baseline information on RNAi-based GM plants (Paces et al, EFSA supporting publication 2017), the degree and position of base-pairing between the small RNA and RNA transcript is the primary factor determining the efficiency of silencing (Liu et al, 2014). Therefore, in silico target prediction algorithms are designed based on the binding energy and base-pairing among other specific filtering parameters (Pasquinelli, 2012, Rhoades et al. 2002). In addition, other factors can influence the potential for this interaction to result in a silencing effect. Among them, the most important is the abundance of each small RNA produced.

Based on the current knowledge, the GMO Panel has laid down the following considerations to deal with small RNA off-target bioinformatic analysis (complementarity searches) in plants.

1. Considerations on how the search has to be done

The applicants will be requested to report on possible off-target plant transcripts by all 21nt small RNAs potentially produced complying with all the following rules.[15,16]

- No more than 4 mismatches (complementarity mismatches) with no gap or 3 mismatches and one gap;
- A G:U pair is considered as a mismatch however it counts as half a mismatch;
- Only one single gap can be present either within the target or the small RNA itself;
- Gaps cannot be more than one nucleotide;
- No mismatches/gap at position 10/11 of the small RNA sequence;
- No more than 2 mismatches (or 1 mismatch and a gap) in the first 12 nt at the 5' of the small RNA;
- The minimum free energy of the duplex divided by the minimum free energy of the perfect complement should be greater than 0.75 (Allen et al 2005).

2. Considerations on how the results should be discussed

The risk assessment of the potential misregulation of the off-target transcripts in the plant should be based on:

[15] The criteria for identifying off-target plant transcripts apply for both artificial miRNAs and siRNAs and are based on experiments investigating primarily miRNA-target specificity.
[16] These rules constitute a conservative approach to search for potential off-targets. They are based on the current knowledge and may evolve with the progress of the knowledge in the field.

- the number of different small RNAs showing significant similarity to the same potential off target transcript since recent evidence suggests that the potential for repression of a gene by a small RNA is correlated with the number of different small RNAs that can bind the same targeted gene (Hannus et al, 2014). This number should be indicated. Transcripts with multiple hits should be the prime focus of the assessment. In applications where the GM plant will produce a single small RNA at high doses (e.g. production of artificial miRNA), a single off-target sequence within a gene may also be of relevance.
- the established or predicted function of the potential off-targets that could impact on the safety of the GM plant and/or derived products as food/feed, or in the environment.

3. Considerations on how the GMO Panel will assess the results

The outcome of the analysis above will be discussed taking into account the phenotypic and compositional data. On a case by case basis, and depending on the nature of the potential off-targets, the evaluation may require new data.

References

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