Network on Risk Assessment of GMOs
Minutes of the 8th meeting

Held on 23-24 May 2017, Parma
(Agreed on 16 October 2017)

Participants

- **Network Representatives of Member States (including EFTA Countries):**

Country	Name
Austria	Marion Dolezel, Markus Woegerbauer
Belgium	Katia Pauwels
Bulgaria	Dimitar Djilianov, Tsveta Georgieva
Cyprus	Antri Varnava Tello
Croatia	Nenad Malenica, Sanja Miloš
Czech Republic	Miloslava Navratilova, Jaroslava Ovesna
Denmark	Jan Pedersen
Estonia	Andres Mäe
Finland	Kirsi Törmäkangas, Annikki Welling
France	Emmanuelle Pic
Germany	Wolfram Reichenbecher, Andrea Scheepers, Regina Selb
Greece	Argyrios Boulis
Hungary	Agnes Fejes, Barnabas Jenes
Ireland	Bernie Murray, Patrick O'Mahony
Italy	Roberta Onori, Elena Sturchio
Lithuania	Zygimantas Janeliunas, Odeta Pivoriene
Luxembourg	Luc Schuler
Netherlands	Boet Glandorf, Esther van Leeuwe-Kok, Cynthia van Rijn
Poland	Zbigniew Dabrowski, Slawomir Sowa
Portugal	Beatriz Oliveira
Slovakia	Petra Gerekova
Slovenia	Martin Batic, Bostjan Petelinc
Spain	Carmen Cuadrado, Félix Ortego
Sweden	Staffan Eklöf, Anita Strömberg
United Kingdom	Louise Ball
Norway	Ville Erling Sipinen

- **Hearing Experts**

Petr Svoboda (for item 7.2).

- **GMO Panel Members**

Josep Casacuberta and Antoine Messéan.

- **European Commission:**

Béatrice Marquez-Garrido and Anastasia Pagida (for items 6.1, 6.2 and 6.3 of the agenda) (DG SANTE).

- **Observers:**

Armin Čolaković (Bosnia-Herzegovina), Martin Schrott (Switzerland), and Birgül Guner (Turkey).

- **EFSA:**

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

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Rene Custers (Belgium), Morten Tune Strandberg (Denmark), Merethe Aasmo Finne (Norway) and Felix Nicolescu (Romania) for the entire meeting.

2. Adoption of agenda

The agenda was adopted without changes.

3. Agreement of the minutes of the 7th meeting of the Network on Risk assessment of GMOs held on 31 May – 1 June 2016, Parma

The minutes were agreed by written procedure on 27 March 2017 and published on the EFSA website 29 March 2017.

4. Topics for discussion

4.1 Update from EFSA on GMO applications, mandates and other activities

Irina Olaru, scientific officer of the GMO Unit, presented an overview on EFSA's work on the risk assessment of genetically modified organisms (GMOs), covering four areas: market authorisation applications (hereafter referred to as 'GMO applications'), guidance documents, external mandates, and grants and procurements. She provided information on: the status of GMO applications received under Regulation (EU) No 1829/2003, the types of plant and level of stacking in on-going GMO applications; guidance documents and explanatory notes under development by the EFSA GMO Panel and GMO Unit; recently

finalised and on-going external mandates received from the European Commission (EC); recently finalised and on-going grants and procurements.

There were no questions after the presentation.

4.2 Risk assessment of subcombinations of stacked GM events

Elisabeth Waigmann, Head of the GMO Unit, presented the GMO Panel's approach to assessing subcombinations.[1] She started by indicating that the assessment of subcombinations, independently of their origin, is a requirement of the Implementing Regulation (EC) No 503/2013 (hereafter referred to as 'IR 503/2013'), and added that the term 'subcombination' refers to lower stacks containing combinations of up to N-1 of the events present in a stack (containing N events), which can be obtained by segregation in the progeny of the stack or through targeted breeding programs, by conventional crossing. She explained that subcombinations obtained by segregation in the progeny of the stack (e.g. F2 generation in harvested grains/seeds) are not intended to be further propagated and are an integral part of the assessment of the stack, therefore need no further consideration. Subcombinations obtained through targeted breeding programs are stacks in themselves, they can be bred, produced and marketed independently of the higher stack, therefore a strategy to assess these subcombinations needs further consideration. This strategy should encompass intended and unintended effects, as for any other stack. A challenge in this context is that for (some of) these subcombinations no specific experimental data would be available. She presented the strategy developed by the GMO Panel, which relies on the risk assessment of the singles, the risk assessment of the stack, previous risk assessments of some of these subcombinations, if available, and on specific data that may be required on a case-by-case basis, and explained how this strategy would be applied.[3]

After the presentation, Staffan Eklöf (Sweden) welcomed the described strategy for being hypothesis-driven. Jan Pedersen (Denmark) asked how an applicant can foresee what type of additional data might be requested during the risk assessment, and for which subcombination. EFSA replied that applicants already have the possibility to offer a rationale for not providing experimental data for subcombinations, which is in line with IR 503/2013, and that the strategy document helps applicants by bringing guidance for the assessment of subcombinations.

4.3 Explanatory note on literature searching conducted in the context of GMO applications

Yann Devos, scientific officer of the GMO Unit, presented the explanatory note to the guidance on literature searching (EFSA, 2017). This explanatory note clarifies the scope and methodology for literature searching performed in the context of GMO applications submitted under Regulation (EC) No 1829/2003 *before* and *after* the IR 503/2013 entered into force; annual post-market environmental monitoring (PMEM) reports on GMOs authorised in the EU market; and GMO applications for the renewed market authorisation of GM food/feed

[1] For further details, please see Annex 1 of Minutes of the 115th plenary meeting of the GMO Panel https://www.efsa.europa.eu/sites/default/files/event/170517-m.pdf

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, thereby complementing previous guidance by EFSA and its GMO Panel (i.e., EFSA, 2010).

Specific recommendations for: (1) identifying review questions and clarifying their purpose; (2) searching for/identifying relevant studies; (3) selecting studies; (4) extracting high level data from the relevant studies, where appropriate; and (5) summarising and reporting the data, and considering the implications of the findings, were presented.

Yann Devos explained that the explanatory note is intended to provide a more rigorous and standardised approach to literature searching in the context of (renewal) GMO applications and annual PMEM reports. It aims to assist applicants to perform more consistent and sensitive literature searching, and ensure that as many relevant studies as possible are retrieved to minimise biases such as publication bias. It was noted that the explanatory note may be revised when experience is gained during its implementation and in view of any amendments to the IR 503/2013.

The presentation was followed by a general discussion on the presented EFSA explanatory note. Emmanuelle Pic (France) asked how EFSA is currently appraising the quality of systematic literature reviews in the context of GMO applications. According to Article 6(1) of the IR 503/2013, "the application shall include a systematic review of studies published in the scientific literature and studies performed by the applicant within the period of ten years prior to the date of submission of the dossier on the potential effects on human and animal health of the GM food and feed covered by the application". This mandatory requirement applies to all GMO applications submitted for regulatory review under Regulation (EC) No 1829/2003 *after* 8 December 2013. However, EFSA indicated that no systematic literature reviews have been submitted to EFSA yet; applicants are of the opinion that it is not useful or necessary to perform the complete systematic literature review process, because the evidence base for new GMOs is limited or non-existent, or that the scientific uncertainty around a topic is low. Instead, applicants have been conducting systematic/extensive literature searches. The quality of these literature searches has been appraised by EFSA using EFSA's critical appraisal tool (CAT) (see Appendix D of EFSA, 2015). The CAT focuses on two aspects of literature searching: (a) the search strategy; and (b) the information sources used. It was also mentioned that EFSA is organising regular training on systematic literature reviews and their appraisal for its staff and experts, so as to strengthen in-house capacity to apply and appraise such reviews.

Boet Glandorf (the Netherlands) asked why the explanatory note refers to environmental risk assessment given that the IR 503/2013 only gives considerations on food/feed safety assessment. EFSA indicated that the principles outlined in the explanatory note are generic in nature, and therefore applicable to different cases, irrespective of the nature of the submission type. Additionally, it was clarified that, depending on their scope, GMO applications submitted under Regulation (EC) No 1829/2003 *before* and *after* the IR 503/2013 entered into force are subject to an environmental risk assessment.

Martin Schrott (Switzerland) noted that reviews are not necessarily considered relevant according to the eligibility/inclusion criteria given in Table 1 of the explanatory note, though such publications may provide relevant background information. EFSA clarified that it depends on the type of review (i.e., narrative reviews vs. systematic literature reviews which can include a meta-analysis) and whether these reviews present data that are not available from primary research studies. Moreover, it was specified that the eligibility/inclusion criteria to establish the relevance of retrieved studies in Table 1 are examples; none of these criteria are mandatory. It would be up to applicants to develop their criteria, justify the choices made, and report these criteria clearly using Table 1 as template.

Following a question from Louise Ball (United Kingdom), it was confirmed that the relevant and reliable studies retrieved via systematic/extensive literature searches can inform problem formulation, be used to test specific hypotheses about the likelihood and severity of adverse effects, and in some instances might replace studies commissioned/performed by applicants during product development/characterisation, in order to support of the risk assessment.

Andrea Scheepers (Germany) asked whether the explanatory note gives specific recommendations on how to formulate review questions not only with regard to form but also with regard to content (i.e.: does the explanatory note aim for a harmonisation of the review questions with regard to contents and/or give specifications on what needs to be addressed in terms of content?), and how to develop and structure search strategies. EFSA clarified that a harmonisation in terms of content is not explicitly foreseen. Applicants are encouraged to specify the problem that the review is addressing in the form of clear, unambiguous and structured questions before the review begins. Given that the focus is on summarising the breadth and type of evidence, review questions should be broad in nature, but with a clearly articulated scope of inquiry. Subsequently, review questions should be broken down into their key elements, in order to guide the development of search terms, structure the search, and inform the selection of relevant studies. Applicants are therefore requested to identify and specify the key elements to formulate relevant and focused review questions. Depending on the type of questions, these elements might include among others "Population(s)" [P], "Intervention(s)" [I] or "Exposure" [E], "Comparator(s)" [C], and "Outcome(s)" [O], and each key element used must be specified in detail. Review questions can also be represented by the categories of information/data requirements outlined in relevant GMO Panel guidance documents, EFSA explanatory notes and the IR 503/2013 (see Appendix A of the explanatory note for an overview). Studies relevant to the (renewal) GMO applications and annual PMEM reports are those that inform one or more information/data requirement(s) for the GMO under consideration (including the intended trait(s), and derived food/feed products).

It was also specified that Appendix B of the explanatory note provides four different examples of how to develop and structure search strategies. Each example presents: (1) the key elements involved in the search and candidate search terms/keywords; (2) the search structure expressed as concepts linked with Boolean operators; and an example search strategy for the Web of Science interface.

4.4 Draft guidelines on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) No 1829/2003

Anna Lanzoni, scientific officer in the GMO Unit, presented an update on the draft guidelines on possible derogation of existing requirements for applications of GM food and feed at low levels submitted under Regulation (EC) No 1829/2003 (named 'Draft guidance for the risk assessment of the low level presence of genetically modified plant material in imported food and feed under Regulation (EC) No 1829/2003', and hereafter referred to as 'LLP GD'), touching on the following points: status of progression of the project plan and schedule; the stakeholders engagement, with a particular focus on EU Member States consultation; and the key points of the draft LLP GD. The mandate was received by EFSA in 2014 and, after a clarification request to EC, was accepted in 2015. The LLP Working Group had the kick-off meeting in November 2015, and the first draft of the LLP GD was submitted for a dedicated consultation period with EU Member States in October 2016. Following this phase, the draft LLP GD was updated and endorsed by the GMO Panel in April 2017, after which the draft guidance was submitted for public consultation, currently on-going at the time of the GMO Network meeting. Following the public consultation, the draft LLP GD will be updated and proposed for discussion and possible adoption at the September 2017 GMO Panel plenary meeting. Related to the EU Member State consultation phase, Anna Lanzoni acknowledged the involvement of EFSA's Advisory Forum and EFSA's National Focal Points, which served as intermediaries in distributing the draft document and collecting comments from Competent Authorities of Member States. As for the key points of the updated draft LLP GD, Anna Lanzoni indicated that, on the basis of comments received by Member States, the scope, definitions and scientific drivers of the LLP GD have been clarified, and explained the main derogations from the IR 503/2013 included in the updated draft LLP GD and the approach proposed by this guidance for environmental risk assessment.

The presentation was followed by a general discussion.

Esther Kok (the Netherlands) asked why the requirements for assessment of newly expressed proteins in LLP GMO events are similar to those for regular applications, although the overall exposure to the respective proteins is lower and for these cases available data may be sufficient to conclude on safety aspects. EFSA answered that the hazard identification and the characterisation of the newly expressed proteins (structure, function) and levels in edible plant parts should be known in order to conduct the risk assessment, even in the case of LLP GMOs.

Emmanuelle Pic (France) wished to have more details on how the cumulative risk assessment will be conducted. EFSA explained that the risk assessment frame is targeted to maximum 0.9% exposure to the GMO subject of the LLP application; in the case of multiple LLP GMOs with the same output trait, for example, the compound linked to that output trait could accumulate to a level significantly above that of the individual LLP GMOs. 0.9% threshold is exceeded in the plate of consumers. This should be taken into account – however, it was remarked that it is difficult to foresee how many LLP applications will be submitted for GMOs with the same output trait, and that this overview will be available at risk manager levels.

Markus Woegerbauer (Austria) expressed his appreciation towards EFSA and the GMO Panel for developing the draft guidance on LLP in close partnership with Member States, indicating that the comments from Austria had been addressed in the updated draft text. He asked why some introductory considerations have been removed from the original version; EFSA replied that this was related to the necessity to simplify and lean the introductory text, following comments received from Member States, and that part of the introduction has been moved to Annex 1 of the draft guidance (namely main differences between the scope of this guidance and the requirements of Codex Alimentarius on LLP). He also asked whether a request for compositional data for LLP GMO events would need all three triggering elements (namely: the intended trait targets the composition of the LLP GMO; a hypothesis for a relevant compositional change can be formulated based on the available information from the hazard identification; and compounds are produced *de novo* in the LLP GMO), to which EFSA replied that one element would be enough to trigger the need for compositional data. Boet Glandorf (the Netherlands) expressed the view that in addition to the agronomic and phenotypic data, horizontal gene flow should also not be mandatory for the environmental risk assessment of GM plants under LLP conditions, given the fact that horizontal gene transfer is very unlikely to occur and is even more unlikely to occur under LLP conditions. EFSA referred to the IR 503/2013, which states that the environmental risk assessment of GMOs or food/feed containing or consisting of GMOs should be performed according to the principles outlined in Annex II to Directive 2001/18/EC on the deliberate release into the environment of GMOs, and applicable GMO Panel guidance documents. The GMO Panel therefore recommends applicants to follow the principles and approach outlined in the GMO Panel guidance document on the environmental risk assessment of GM plants (EFSA GMO Panel, 2010) to determine the data requirements for ERA of GM plants under LLP situations. Like for standard GMO applications for food/feed uses, for import and processing, the environmental risk assessment of GM plants under LLP conditions should consider exposure of microbial communities to recombinant DNA in the gastrointestinal tract of animals fed GM plant material or recombinant DNA in faecal material (manure and faeces) of these animals. This exposure pathway needs to be taken into account in the problem formulation.

Jan Pedersen (Denmark) indicated that, considering the proportion of the LLP event in the ingredient, very high levels of a certain compound from the LLP GMO would be needed in order to reach a level of concern in the overall ingredient. EFSA explained that, as described in Table 1 of the draft GD, a 100-fold increase of a compound in the LLP event would lead to a 2-fold increase of the respective compound in the overall ingredient, and for certain compounds this increase could give rise to a concern. Slawomir Sowa (Poland) agreed that, for this reason, the case-by-case approach in the assessment of LLP GMOs would be most fitting.

Annikki Welling (Finland) asked whether applicants would be required to provide an event-specific detection method for each LLP GM event, to which EFSA answered that the detection aspect is not within the remit of EFSA.

5. Break-out session Molecular Characterisation / Food-Feed Safety

5.1 Supplementary guidelines for the allergenicity assessment of GM plants

Antonio Fernandez-Dumont, scientific officer of the GMO Unit, presented the supplementary guidance document on allergenicity assessment of GMOs. This guidance document is the result of a self-task activity initiated by EFSA to consider new scientific and regulatory developments in the area of allergenicity. In particular, this document addresses three main topics: i) non-IgE-mediated adverse immune reactions to food; ii) *in vitro* protein digestibility tests; and iii) endogenous allergenicity. For non-IgE-mediated adverse immune reactions to food, detailed risk assessment considerations are provided to determine the safety profile of the protein or peptide under assessment with regard to its potential to cause celiac disease. This assessment should include available information on the source of the transgene and on the protein itself, as well as data from *in silico* and *in vitro* testing, if appropriate. For *in vitro* protein digestibility tests, it is considered that additional investigations are needed before any additional recommendation in the form of guidance for applicants can be provided. To this end, an interim phase is considered necessary to evaluate the revisions to the *in vitro* gastrointestinal digestion test, proposed by EFSA, which are presented in an Annex to the guidance document. For assessing endogenous allergenicity of GM plants and to support the practical implementation of mandatory requirements in IR 503/2013, the guidance document provides further information on: i) relevant crops subjected to such analysis; ii) relevant allergens that should be quantified; iii) methodology to be used for quantification; and iv) principles to be followed for data interpretation and risk assessment considerations.

EFSA strengthened new means of engaging with stakeholders from the initial stages of guidance development, in order to enhance both the quality of the EFSA guidance document and the communication with stakeholders and the general public. This was done through a "Focus group" interactive consultation body that closely followed the development of the document.

The presentation was followed by a general discussion. Esther Kok (the Netherlands) expressed her appreciation for the revised document. Jan Pedersen (Denmark) asked how to determine natural variation for endogenous allergens from a broader perspective than the current EFSA field trial design. EFSA replied that a first attempt in this direction is proposed in the new guidance document, where the standardisation and harmonisation of the analytical methods used among applicants would be beneficial to enhance measurement comparability. This would support the possible future establishment of a database on expression levels of allergens, which would give an indication of natural variation and improve the robustness of the safety assessment.

Emmanuelle Pic (France) asked whether OECD plans to develop a document on other plants than soybean, maize, oilseed rape, to which EFSA replied that such initiatives should start from the Members of OECD. Anita Strömberg (Sweden) asked whether endogenous allegenicity was considered for crops other than soybean, to which EFSA replied that to date EFSA considers endogenous allergenicity risk assessments based on experimental data for foods recognised

to be common food allergens and of public health importance, as listed in Annex II of the European Regulation on food information to consumers (e.g. soybean).[2] However, the example provided on how to identify and select allergens, and interpret results for soybean in the Annex C of the guidance document may be used for other crops than soybean in the future, if considered necessary. For these considerations, risk assessors, risk managers, health professionals and stakeholders can provide valuable feedback.

5.2 Explanatory note on Next Generation Sequencing (NGS) for the characterisation of GM plants

Nikoletta Papadopoulou, scientific officer of the GMO Unit, presented EFSA's draft explanatory note on the analysis of DNA insertion sites and generational stability in the genetically modified plant by Next Generation Sequencing (NGS), using a junction read analysis approach. EFSA is currently elaborating this note and has consulted experts from the GMO Panel's Molecular Characterisation (MC) WG in the process. Junction read analysis using data obtained from NGS is a method used in recent GMO applications, as an alternative to Southern blot, for the analysis of insertion sites of DNA intended to be inserted into the GM plant genome as well as the identification of any insertion of vector DNA. In addition, junction read analysis can be used for the assessment of genetic stability of the inserted DNA across generations. In this explanatory note, EFSA provides recommendations on the information to be submitted in the context of GMO applications, so that EFSA can perform its assessment in a standardised manner.

The presentation was followed by a general discussion. Jan Pedersen (Denmark) asked about the minimum read depth, the reference gene to be used and the questions to be answered by junction read analysis using data obtained from NGS. EFSA replied that the applicant should indicate and justify the read depth, which in principle should be at least 75×; however, this will not be uniform across the entire genome. Josep Casacuberta, member of the GMO Panel, added that applicants have been using NGS mainly to characterise the insertion sites, and to check if any backbone fragments have been inserted during the transformation process, as an alternative to Southern blot. It is the free choice of the applicants to use NGS to address different aspects of the molecular characterization of the GM plant.

Esther Kok (the Netherlands) asked whether NGS would replace Southern analysis and whether the NGS data would be used to identify unintended changes in the genome. EFSA clarified that this explanatory note does not suggest replacing Southern analysis or Sanger sequencing with NGS, it only gives guidance on the information that applicants should provide to EFSA when using NGS to support the molecular characterisation of the GM plant, leading also to the harmonisation of data submitted by applicants. EFSA noted that the assessment strategy has not changed in light of new available techniques like NGS.

[2] Regulation (EU) No 1169/2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004

Emmanuelle Pic (France) asked whether the sequence comparison should be done with the reference genome or with the near isogenic line (conventional comparator). Josep Casacuberta reminded that if NGS is used to characterise the insertion site and flanking regions, than the flanking regions should be compared with the preinsertion locus in the near isogenic line.

Slawomir Sowa (Poland) commented that reference genomes are not available for all GM plants, so in order to ensure the 75× coverage applicants could use also the conventional counterpart, to which EFSA replied that the absence of a reference genome may pose a problem for applicants in certain cases, but the 75× coverage can be demonstrated even in the absence of the reference genome, so this will be the minimum coverage acceptable. EFSA also reminded that the applicant should document how the analysis was performed and how the data was processed.

Jan Pedersen (Denmark) asked what the minimum size of inserted backbone fragment relevant for the risk assessment is. EFSA replied that any insertion of backbone sequence should be risk assessed; Josep Casacuberta added that this is in line with the IR 503/2013, and that the assessment strategy of the GMO panel has not changed.

6. Break-out session Environmental Risk Assessment

6.1 Assessment of the representativeness of field trial sites

Andrea Gennaro and Giacomo De Sanctis, scientific officers of the GMO Unit, presented EFSA's approach to assess the representativeness of field trial sites used for the agronomic/phenotypic and compositional characterisation of GM plants. Both the IR 503/2013 and the EFSA GMO Panel guidance on risk assessment of food/feed from GM plants (EFSA GMO Panel, 2011) require the selection of representative field trial sites. Practical recommendations on how to select appropriate sites, which should be sufficiently diverse in terms of meteorological and soil characteristics and which should remain inside the geographical limits where the GM plant will be grown, are given in the EFSA GMO Panel guidance on agronomic and phenotypic characterisation of GM plants (EFSA GMO Panel, 2015). During the presentation, the two scientific officers provided hypothetical examples on how to select representative sites based on the geographical location and meteorological and soil characteristics of sites, complementing the examples given in EFSA GMO Panel (2015). The evaluation of these characteristics requires a multi-factor analysis, and is based on the land suitability classification developed by FAO (1976) which has been implemented subsequently by Sys et al. (1993). According to this approach, the main climatic and soil requirements specific for each crop are divided in different classes, which reflect potential crop productivity. Those classes indicate: optimal growing conditions; near-optimal growing conditions; suboptimal growing conditions; marginal growing conditions; non-suitable conditions but susceptible to correction; and non-suitable conditions, specific for each requirements. Graphical representations of the multi-factor analyses were also presented. The approach followed by EFSA should guide applicants when selecting field trial sites, while the proposed selection criteria will increase the transparency and the repeatability of this assessment.

Kirsi Törmäkangas (Finland) asked how the proposed approach accounts for altered farm management practices due to climate change, and whether the baseline is expected to evolve over time. EFSA clarified that it is unlikely that climate change will substantially impact the categories used. However, crop maturity ranges and possibly also precipitation patterns may shift. EFSA indicated that the limits of the classification should not be considered fixed. Instead, these limits give an indication of wide ranges. Expert judgement will remain key to interpret the graphical representations.

Boet Glandorf (the Netherlands) considered that the representativeness of the field sites is dependent on the purpose of the trials and what needs to be studied. The presented approach may be useful for the agronomic/phenotypic assessment of unintended effects, but less for intended effects or effects on, for example, specific non-target organisms; in that case, the field sites and experimental set-up should be designed on a case-by-case basis. EFSA replied that the meteorological and soil characteristics of field trials should be given for the agronomic/phenotypic sites as well as for those sites used for the compositional characterisation in case applicants generate compositional data in different field trial locations than those performed for the agronomic/phenotypic characterisation of GM plants. EFSA also indicated that the field trials are not only designed to detect unintended effects, but also the intended ones.

Boet Glandorf (the Netherlands) subsequently asked how pest and disease pressure is considered in this assessment. EFSA referred to EFSA GMO Panel (2015), as it provides specific recommendations on this point.

Zbigniew Dabrowski (Poland) expressed concerns about the approach, because it is mostly based on US data and may be more challenging to implement for cultivation conditions in the EU. EFSA indicated that this approach has been developed mainly for GM plant applications for import and processing for food/feed uses, and that it needs to be adapted in case of GM plant applications for cultivation.

Wolfram Reichenbecher (Germany) was pleased to note that EFSA is elaborating an approach and criteria to assess field trial site representativeness, as this will ensure more transparency and consistency. He then requested clarifications on where the graphical representation of site classification and the methodology used will be published. EFSA replied that the examples will be annexed to EFSA's guidance on the submission of applications for authorisation of GM plants under Regulation (EC) No 1829/2003 that will be subject to an update (EFSA, 2013).

Staffan Eklöf (Sweden) stated that the term representativeness is problematic, but welcomed the proposed approach for GM plant applications for import and processing for food/feed uses, but underlined that the approach cannot be transferred to cultivation and ecological interactions, due to the high number of different variables and the huge complexity.

Marion Dolezel (Austria) stated that the geographical origin of grain imports derived from GM plants should be one of the main criteria to consider when assessing the representativeness of field trial sites. In this context, Antoine Messéan, member of the GMO Panel, indicated that data transportability should be considered, as the geographical origin of GM grain imports may evolve over time. It was also acknowledged that this is a challenging point as

geography is only one of the criteria used to assess the field trial site representativeness.

6.2 EFSA GMO Panel scientific opinion on the 2015 annual PMEM report for maize MON810

Fernando Álvarez, scientific officer of the GMO Unit, presented the latest EFSA GMO Panel scientific opinion on the annual PMEM report on the cultivation of GM maize MON810, corresponding to the cultivation season 2015 (EFSA GMO Panel, 2017). During his presentation, Fernando Álvarez informed participants on the status of the cultivation of maize MON810 in the EU, gave an overview of the case-specific monitoring (CSM) and general surveillance activities (GS) performed by the consent holder, and summarised the conclusions and recommendations made by the GMO Panel in its scientific opinion.

The insect resistance monitoring data do not indicate a decrease in susceptibility of Iberian field populations of the target pests to the Cry1Ab protein during the 2015 season. However, since the methodology for insect resistance monitoring remained unchanged compared to previous PMEM reports, the GMO Panel reiterated its previous recommendations on resistance monitoring to provide sufficient detection sensitivity (i.e., ≤3% frequency of resistance alleles).

The consent holder implemented an alert system allowing farmers to report complaints about product performance (including unexpected field damage caused by target pests). Although the farmer alert system could complement the information obtained from the laboratory bioassays, the GMO Panel encouraged the consent holder to provide more information on this complementary resistance monitoring tool in order to appraise its usefulness.

The data on GS through farmer questionnaires and literature searching do not indicate any unanticipated adverse effects on human and animal health or the environment arising from the cultivation of maize MON810. The GMO Panel reiterated its previous recommendations on the analysis of farmer questionnaires, and advised the consent holder to provide more detailed information on the conducting and reporting of the literature search in future PMEM reports.

The GMO Panel concluded that the CSM and GS activities on maize MON810 as performed by the consent holder do not provide evidence that would invalidate previous GMO Panel recommendations on the safety of this GM maize. However the GMO Panel identified methodological limitations pertaining to insect resistance monitoring and farmer questionnaires that need further consideration by the consent holder, because the resistance monitoring activities do not provide sufficient sensitivity for an early detection of potential resistance of target pests in the field, and the sampling frame for the farmer questionnaires does not allow the assessment of the representativeness of the results.

The presentation was followed by a general discussion. Wolfram Reichenbecher (Germany) asked whether any of the complaints received in 2015 through the farmer alert system were related to infestation of maize MON810 by corn borers. EFSA clarified that the consent holder reported that none of the complaints were related to unexpected damage caused by corn borers.

Zbigniew Dabrowski (Poland) asked whether there are any reported cases of field-evolved resistance to Cry1 proteins reported for corn borers outside the EU. EFSA replied that there have been reports of field-evolved resistance in some lepidopteran species, such as *Spodoptera frugiperda* in Puerto Rico and *Busseola fusca* in South Africa, but none for *O. nubilalis*. Reasons for these instances of field-selected resistance range from the insufficient planting of refuges of non-*Bt*-maize in South Africa to the autosomal, non-recessive inheritance of resistance by *S. frugiperda* in Puerto Rico, and specific agronomic/environmental factors. South African farmers declared non-irrigated conventional maize as refuges for irrigated *Bt*-maize, which most likely decreased random mating and egg-laying, as moths prefer high humidity. In Puerto Rico, factors that may have contributed to unprecedented levels of selection pressure on *S. frugiperda* populations are: continuous year-round planting of *Bt*-maize; limited migration from external ecosystems (island geography); and drought conditions that concentrated pest populations in irrigated fields.

6.3 EFSA technical report assessing the relevance of new scientific evidence on the occurrence of teosinte in maize fields in Spain and France for previous environmental risk assessment conclusions and risk management recommendations on the cultivation of maize events MON810, Bt11, 1507 and GA21

Yann Devos, scientific officer of the GMO Unit, presented the EFSA technical report assessing the relevance of new scientific evidence on the occurrence of teosinte in maize fields in Spain and France for previous environmental risk assessment conclusions and risk management recommendations on the cultivation of maize events MON810, Bt11, 1507 and GA21 (EFSA, 2016). Following a request of the European Commission[3], EFSA assessed the available scientific information on teosinte for its relevance for the environmental risk assessment of maize MON810, Bt11, 1507 and GA21 for cultivation.

The presence of teosinte in the EU has been reported in maize fields in Spain (in the Ebro Valley (Aragón) and in the region of Cataluña in the summer of 2014) and, to a lesser extent, in France (in the region of Poitou-Charentes since 1990).

It was clarified that teosinte is native to Mexico and Central America, and is considered the direct wild ancestor of maize. In the centres of its origin, teosinte grows commonly as a wild plant, and some of these populations are protected to conserve teosinte as a source of genetic diversity. In some regions, teosinte is grown for forage purposes. Outside its centres of origin, teosinte is not indigenous, but has become naturalised/ established in some countries. In these situations, teosinte does not represent an environmental entity of concern that requires protection. Instead, it is occasionally cultivated for its forage potential, or considered a weed that can compete with cultivated maize in agricultural fields, thereby reducing yield and compromising harvest quality. In infested agricultural fields, teosinte is subject to control and/or eradication measures.

Pathways to harm from the cultivation of maize MON810, Bt11, 1507 and GA21 were hypothesised for situations where maize MON810, Bt11, 1507 and GA21

[3] http://registerofquestions.efsa.europa.eu/roqFrontend/questionDocumentsLoader?question=EFSA-Q-2016-00388

and teosinte would grow sympatrically, focusing on specific areas of risk typically considered in environmental risk assessments of GM plants. For each of these pathways it is unlikely that environmental harm will occur. EFSA therefore concluded that there are no data that indicate the necessity to revise the previous environmental risk assessment conclusions and risk management recommendations for maize MON810, Bt11, 1507 and GA21 made by the GMO Panel. To ensure effective long-term management of teosinte and maize × teosinte hybrids that acquired glyphosate tolerance through vertical gene flow from maize GA21, and avoid exacerbating weed problems, EFSA recommended that integrated weed management reliant on multiple tactics is deployed when growing maize GA21, because the use of glyphosate-based herbicides on maize GA21 may enhance the fitness of glyphosate tolerant maize × teosinte hybrids.

The presentation did not trigger questions and was therefore not followed by a general discussion.

7. Topics for discussion

7.1 Limits of concern in environmental risk assessment

Marion Dolezel, delegate from Austria to the GMO Network (ERA), gave a presentation on the results of a study on Limits of Concern for the environmental risk assessment of GM plants carried out by the Environment Agency Austria. Since the concept of Limits of Concern (hereafter referred to as 'LoCs') for the ERA of GMPs has been introduced by EFSA in its Guidance Document in 2010 it has so far not been implemented by applicants. The study[4] provides a conceptual framework for the implementation of the concept in the ERA of GMPs and highlights needs for improvements and further guidance. By the use of examples possibilities for the operationalisation of the concept are outlined.

The presentation was followed by a general discussion. Boet Glandorf (the Netherlands) commented that there should be a clear distinction between the scientific and political aspects determining the interpretation of the LoCs; she also expressed the view that setting transparent, clear and fixed LoCs is not prevented by the lack of knowledge, but by the ecological complexity of the issue, giving the example of non-target organisms. Marion Dolezel replied that political considerations may be taken into account in the decision-making process in the absence of certain scientific information (e.g., the safe ecological limits). She indicated that using political decisions in combination with scientific knowledge to set thresholds is a common practice in other regulatory areas, such as plant protection products, and concluded that setting LoCs based on science alone will be hardly feasible. To the second comment, she replied that trigger values should be established before starting the risk assessment, like is the case in other regulatory areas.

Jan Pedersen (Denmark) wondered how non-equivalence between a GM plant and its conventional counterpart would constitute a trigger for harm, considering that also conventional varieties may influence the environment. He therefore questioned how normal variation of crop plants fits into the concept of LoCs. Marion Dolezel replied that non-equivalence refers to those cases for which the

[4] For further reading, please see https://enveurope.springeropen.com/articles/10.1186/s12302-017-0104-2

GM plant is both different from the comparator and, at the same time, falls outside the range observed in the reference varieties. In her opinion, this situation should be further assessed to check whether there is a consequence to the protection goal.

Staffan Eklöf (Sweden) noted that recovery and migration should be taken into account when deciding LoC, as these species-specific aspects may contribute significantly to establishing the acceptable mortality rate; he gave the example of species with the majority of individuals being at reproductive stage, which would translate into the capacity to overcome very high (up to 90%) mortality rates, while for other species even low mortality rates would have considerable consequences. Marion Dolezel agreed that this is a very important point and there has to be species-specific differentiation of acceptability thresholds.

Antoine Messéan, member of the GMO Panel, commented that the Scientific Committee is working on the topic of LoCs, and so does the AMIGA Project[5]. He indicated that a statistical difference does not imply biological relevance; just like biological relevance does not imply a concern. Also, they may depend on the characteristics of receiving environments. It is therefore key to translate those and put these into the context of harm. He added that LoCs as discussed in Dolezel et al. (2017) and GMO Panel (2010) cover several concepts which should be clarified, e.g., effect size to interpret small-scale field trials vs limits of concern on ecosystem services at a higher scale.

Slawomir Sowa (Poland) indicated that it is difficult to establish LoCs for each environmental component in each receiving environment, and that it would be important to choose methods capable of detecting small changes; he also commented that the tiered approach can be misleading, and asked when and why additional information would be needed. Marion Dolezel replied that the stepwise approach is embedded in Directive 2001/18, and that she considers it suitable. She noted that laboratory bioassays may serve different purposes, and answer different questions than field studies.

7.2 Baseline information to support risk assessment of RNAi-based GM plants

Petr Svoboda, associate professor at the Institute of Molecular Genetics of the Academy of Sciences of Czech Republic, presented the outcome of an EFSA procurement[6] aiming at investigating and summarising the state of knowledge on (I) the mode-of-action of dsRNA and miRNA pathways, (II) the potential for non-target gene regulation by dsRNA-derived siRNAs or miRNAs, (III) the determination of siRNA pools in plant tissues and the importance of individual siRNAs for silencing. The procurement is based on a comprehensive systematic literature search, starting with the identification and retrieval of~190,000 publications related to the research area and further filtered down with keywords to produce focused collections used for subsequent screening of titles and abstracts. The outcome of the first task reviews dsRNA and miRNA pathways in mammals (including humans), birds, fish, arthropods, annelids, molluscs, nematodes, and plants. Eight taxon-dedicated chapters are based on ~1,400

[5] For more details, please see http://www.amigaproject.eu/

[6] For more details, please see http://www.efsa.europa.eu/en/supporting/pub/1246e

cumulative references chosen from ~10,000 inspected titles and abstracts. Conserved and divergent aspects of small RNA pathways and dsRNA responses are reviewed, in animals and plants, including structure and function of key proteins as well as four basic mechanisms: genome-encoded post-transcriptional regulations (miRNA), degradation of RNAs by short interfering RNA pools generated from long dsRNA (RNAi), transcriptional silencing, and sequence-independent responses to dsRNA. The outcome of the second task focuses on base pairing between small RNAs and their target RNAs and predictability of biological effects of small RNAs in animals and plants. The outcome of the last task reviews methodology, siRNA pools, and movement of small RNAs in plants. Potential transfer of small RNAs between species and circulating miRNAs in mammals is described in the final chapter.

Barnabas Jenes (Hungary) asked about the half-life of dsRNA, to which Petr Svoboda replied that it would depend on the experiment and on the chemical modifications of the dsRNA, its half-life would be of 2-3 days but half-life would be influenced if dsRNA is modified to reduce degradation.

Boet Glandorf (the Netherlands) asked whether it can be concluded that the importance of off-target effects of siRNA lies more in the environmental risk assessment area than in that of food-feed safety. Petr Svoboda confirmed that food and feed contain vast amounts of small RNAs, therefore humans and animals are exposed to many combinations of small RNAs; he indicated that, for humans, intolerance to a certain food has not been linked to any food-borne small RNA. He also pointed out that in animals this is post-transcriptional, transient regulation, so in the absence of the triggering small RNAs, the effects would disappear within 72 hours. Josep Casacuberta, member of the GMO Panel, added that risk assessment should have a different approach for insects, compared to that for humans and mammals, and also make a clear distinction between dsRNAs and artificial microRNAs; he also indicated that the EFSA GMO Panel MC WG is currently working on a set of rules for assessing the potential off-targets of RNAi as required by IR 503/2013.

Related to the comment that RNAi should be assessed in a species-specific manner, EFSA asked how the assessment should be done for birds, since they were not included in the presentation, to which Petr Svoboda replied that birds have the same system as mammals, from the RNAi point of view.

7.3 Omics technologies used to identify potential unintended effects in GM plants

Esther Kok, delegate from the Netherlands to the GMO Network (MC/FF), presented omics and bioinformatics applied to the characterisation of plant materials. The safety assessment of new GM varieties currently relies on both compositional analysis and animal feeding studies; one of the main goals of these analyses is detecting unintended effects of the genetic modification in a more sensitive way than is currently feasible. The compositional analysis includes the GM variety and its conventional counterpart, and other conventional varieties, and has a targeted approach – it analyses key nutrients and anti-nutrients, including natural toxins. Unlike the targeted approach of compositional analyses, omics provide a broader picture of the plant under assessment, by providing information on the transcriptome (all transcribed DNA products),

proteome (all proteins) and metabolome (all secondary products). Two main advantages of omics analyses are: i) thousands of endpoints are analysed, compared to only few hundreds of endpoints assessed in the classical comparative assessment; and ii) there is a broad coverage of individual metabolic pathways, unlike the limited coverage offered by targeted analyses. However, omics bring new challenges to the discussion: as more endpoints are analysed, more differences will be observed, so the interpretation of the results in the context of risk assessment and safety is important. In order to interpret such data, Wageningen UR Institute and University of Nijmegen propose the use of safe classes, which are created to take into account natural variation; the basic criterium for this approach is that if the profile of a new GM plant falls within the safe class for the respective plant, the GM plant should be safe.

The presentation was followed by a general discussion. Jaroslava Ovesna (Czech Republic) asked whether the presented approach is applicable for both food-feed safety and environmental risk assessment, and whether these data would help speed up the evaluation of applications. Esther Kok replied that if the profile of a GM plant fits in a safe class, it is very unlikely that the plant would be unsafe; this rule would be applicable for both food/feed safety assessment and environmental risk assessment. Boet Glandorf (the Netherlands) added that omic profiles are not yet considered to be applicable for the environmental safety since it is unclear how differences in profiles relate to potential environmental risks. Moreover, it would be difficult to say in advance which plant parts or which developmental stages to assess. To the second question, EFSA replied that it would be difficult to say if the evaluation will be finalised earlier.

Staffan Eklöf (Sweden) asked how variation between individuals is dealt with and whether there are species for which intra-specific variation was found to be an issue. Esther Kok replied that intra-specific variation is included in the model and that material was collected from different genotypes, different harvests, different soils.

Jan Pedersen (Denmark) asked if a certain endpoint, like lectins or vitamin B, can lead to the GM plant being outside a class, to which Esther Kok replied that omics provide a different type of information, moving from single endpoints to a broad overview, but it is assumed that if the levels of individual compounds become highly aberrant, outside of normal values for the species, this will be observed in this model. This has, however, not been put to the test yet.

Antoine Messéan, member of the GMO Panel, asked whether the comparison with the conventional counterpart would still be used by the omics approach, and if omics could be used to check any variety a certain GM event would be introduced in. Esther Kok replied that this approach implies the comparison with a general class of reference varieties and agreed that the varieties which are used in the one safe class should be commercial varieties. This approach may reduce the necessity to make the direct comparison with the conventional counterpart, also because it will be increasingly difficult to identify the best comparator.

Josep Casacuberta, member of the GMO Panel, commented that powerful methods have the downside of detecting artefacts and false positives, and that processing of the data may have consequences on the results; he asked whether omics could be used to complement currently used methods in risk assessment

of GMOs, indicating that these methods are good for assessing natural variability. Esther Kok replied that, for transcriptomics, the data from test samples and from reference varieties used to create the safe class is processed in the same way, therefore this step should not compromise the final results. The first step in the transcriptomics approach is a strict quality check, which will result in most artefacts being removed from the assessment. As for omics uses in the risk assessment of GMOs, she indicated that if significant differences are identified by application of the one class model, further information might be obtained through further analysis of the available omics data; she added that, although omics may not immediately replace the currently applicable targeted approach, she hopes that this will be possible in the future once it has been shown that omics analysis is at least as informative as comparable targeted analysis.

EFSA asked which varieties were included in the construction of the one safe class in the model, and Esther Kok replied that only commercial varieties were included in the safe class.

7.4 Living Modified Organisms and synthetic biology

Boet Glandorf, delegate from the Netherlands to the GMO Network (ERA), presented the Cartagena protocol on biosafety and the relation to synthetic biology that is discussed as an emerging issue under the Convention on Biological Diversity (CBD).[7] She started by providing the background of the CBD, created in 1992 and signed by 193 governments (Parties). The main goals of the CBD are: the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of the benefits from the use of genetic resources. The Cartagena Protocol on Biosafety (CP) to the CBD is an international agreement which aims to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking also into account risks to human health. Parties under the CBD and CP meet bi-annually; the last meeting was in December 2016 in Cancun. Since most of the organisms obtained by synthetic biology are considered to be a LMO, there is a clear synergy between the two topics and experts are involved in discussions under both the CBD and CP. In preparation to the next meeting in 2018, discussions on specific topics regarding risk assessment of LMOs and synthetic biology will take place via an online forum. Member State experts are invited to join this online forum. Martin Batic (Slovenia) added that experts can be appointed through national Focal Points, to participate to the online forum. He commented that operational definitions are needed at EU level and that further guidance documents will come under the Cartagena protocol.

Slawomir Sowa (Poland) added that the Polish Ministry of Environment is currently looking into the research done on synthetic biology and to the potential impact on biodiversity.

[7] For more details, please see https://www.cbd.int/

8. Any Other Business

8.1 Panel renewal

Elisabeth Waigmann informed the GMO Network experts that EFSA is renewing its scientific panels[8] and encouraged the participants to apply and/or to share the information with fellow scientist in their home countries.

8.2 Date for next meeting

Irina Olaru proposed to have the 2018 GMO Network meeting at the end of May or beginning of June 2018; she informed the GMO Network experts that the tentative dates for the meeting will be communicated in December 2017 and the final date will be confirmed in February 2018.

8.3 Renewal of the Terms of Reference

Irina Olaru referred to the 'Updated Terms of Reference' document that had been sent to the GMO Network experts before the meeting and asked whether they had any comments; no comments were received. She informed that the document will be submitted to the Advisory Forum, for approval.

8.4 Upcoming events

Irina Olaru provided information on upcoming events, such as the 2017 GMO Panel open plenary meeting (25-26 October 2017)[9] and EFSA's 3rd Scientific - Conference (third week of September 2018), and encouraged the GMO Network experts to browse the EFSA website pages on: open consultations on EFSA documents[10], which includes the LLP GD presented under item 4.4 of the current meeting; grants and procurements[11], where the call for detection and quantification of allergens in foods and minimum eliciting doses in food allergic individuals is listed, but also other general calls; and on the EU-FORA fellowship programme[12], which offers a unique opportunity to motivated early to mid-career scientists from EU national risk assessment authorities and any other Article 36 organisation to increase their knowledge and experience in food safety risk assessment.

9. Conclusions

Elisabeth Waigmann thanked the GMO Network experts for the active participation and the fruitful discussion, the speakers for the interesting topics proposed and excellent presentation, the GMO Panel members for contributing to the scientific exchange, and to EFSA staff for organising and contributing to the meeting.

10. Closure of the meeting

8 http://www.efsa.europa.eu/en/press/news/170601
9 http://www.efsa.europa.eu/en/stakeholders/observers
10 http://www.efsa.europa.eu/en/calls/consultations
11 http://www.efsa.europa.eu/en/calls/art36grants
12 http://www.efsa.europa.eu/en/engage/fellowship

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Abbreviations

CAT	Critical appraisal tool
CBD	Convention on Biological Diversity
CP	Cartagena Protocol on Biosafety
CSM	Case-specific monitoring
DNA	Deoxyribonucleic acid
EC	European Commission
EFSA	European Food Safety Authority
EFTA	European Free Trade Association
ERA	Environmental risk assessment
EU	European Union
FAO	Food and Agriculture Organisation
FF	Food-Feed
GD	Guidance document
GMO	Genetically modified organism
GS	General surveillance
IgE	Immunoglobulin E
IR 503/2013	Implementing Regulation (EU) No 503/2013
LLP	Low level presence
LMO	Living modified organism
LoC	Limits of concern
MC	Molecular characterisation
NGS	Next generation sequencing
PMEM	Post-market environmental monitoring
(ds/mi/si)RNA(i)	(double stranded/micro/small interfering) ribonucleic acid (interference)
WG	Working group