Network on Risk Assessment of GMOs
Minutes of the 9th meeting

Held on 8-9 November 2018, Parma
(Agreed on 28 November 2018)

Participants

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

Country	Name
Austria	Marion Dolezel, Markus Wögerbauer
Belgium	Didier Breyer
Bulgaria	Dimitar Djilianov, Tsveta Georgieva
Cyprus	-
Croatia	Nenad Malenica
Czech Republic	Jaroslava Ovesna
Denmark	Jan Pedersen
Estonia	Teele Jairus, Andres Mä
Finland	Kirsi Törmäkangas, Annikki Welling
France	Nathalie Arnich, Catherine Golstein, Emmanuelle Pic
Germany	Hermann Broll, Mathias Otto, Andrea Scheepers
Greece	Dionysia Stefanitsi
Hungary	-
Ireland	Patrick O'Mahony
Italy	Roberta Onori, Elena Sturchio
Latvia	Lelde Grantina-Ievina
Lithuania	Vaclovas Jurgelevicius
Luxembourg	Luc Schuler
Malta	-
Netherlands	Boet Glandorf, Esther Kok
Poland	Slawomir Sowa
Portugal	Márcia Reto
Romania	Felix Nicolescu
Slovak Republic	Petra Vanková
Slovenia	Bostjan Petelinc
Spain	Carmen Cuadrado
Sweden	Anita Strömberg, Sabá Wallström
United Kingdom	-

Norway	Ville Erling Sipinen
Switzerland	Martin Schrott

- **Hearing Experts**

Wilfried Wackernagel (for item 6.1); Samson Simon (for item 6.2)

- **European Commission:**

Ilaria Ciabatti, Béatrice Marquez-Garrido, Hans Moons (DG SANTE)

- **EFSA:**

GMO Panel: Javier Moreno and Nils Rostoks.

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

SCER Unit: Caterina Barrasso and Reinhilde Schoonjans participated to agenda points 6.1-6.4.

8 November 2018

1. Welcome and apologies for absence

The Chair welcomed the participants.

Apologies were received from Rene Custers (Belgium), Elena Odiatou (Cyprus), and Fruzsina Maté (Hungary) for the whole meeting, and from Catherine Golstein for 8 November.

2. Adoption of agenda

The agenda was adopted without changes.

3. Agreement of the minutes of the 8th meeting of the Network on Risk Assessment of GMOs held on 23-24 May 2017, Parma

The minutes were agreed by written procedure on 16 October 2017 and published on the EFSA website 20 October 2017.

The Chair explained that, in line with the new EFSA procedures related to meeting minutes, the GMO Network experts will receive the minutes shortly after the meeting, with a limited time to provide comments. The timeline will be communicated by e-mail, together with the first draft of the minutes of this meeting.

4. Topics for discussion

4.1 Update from EFSA on 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 and explanatory notes, external mandates,

and grants and procurements. She provided information on: applications received under Regulation (EU) No 1829/2003 (status, types of plant and level of stacking); guidance documents and explanatory notes recently finalised or under development by the EFSA GMO Panel and GMO Unit; external mandates received from the European Commission (EC); and grants and procurements.

Sylvie Mestdagh, scientific officer of the GMO Unit, presented an overview of the consultation held with MS Competent Authorities on GMO applications. In accordance with Articles 6(4) and 18(4) of Regulation (EC) No 1829/2003, EFSA consults the nominated risk assessment bodies of European Union Member States (EU MS), including national Competent Authorities within the meaning of Directive 2001/18/EC, on each request for the placing on the market of a GMO. The EU MS have three months, as of the date of validity of the application at stake, to make their opinions known. At the end of the risk assessment, EFSA makes its opinion, including comments from CAs[1], publicly available according to Articles 6(6) and 18(6) of Regulation (EC) No 1829/2003. EFSA reported on its past years' experience with collecting, reviewing and addressing the comments from MS. Against this background EFSA has identified some room for improvement aiming at the 'optimization' of mutual resources without undermining the level of scrutiny of the comments. The present meeting is therefore an adequate forum to engage a dialogue with MS. Background material was shared prior to the meeting in order to enable MS to consult relevant bodies, if needed, and hence to facilitate the discussion on (1) the relevance of MS comments, and (2) the usefulness of Annex G.

The presentation was followed by a general discussion. Related to (1), GMO Network experts from Austria, Belgium and Denmark agreed with reducing comments that are outside the remit of EFSA's GMO Panel, while confirming the value of EFSA's answers to risk assessment-related MS comments. Didier Breyer (Belgium) suggested EFSA to prepare guidelines on which types of comments fall within the remit of the GMO Panel; this suggestion was also supported by experts from the Netherlands and Norway. Related to (2), experts from Austria and the Netherlands expressed the importance of GMO Panel responses to their comments (as provided in Annex G) in their national risk assessment process. Austria pointed out that this should also to be discussed with the EC and national Competent Authorities in the Standing Committee Meeting.

Anna Lanzoni, scientific officer of the GMO Unit, presented the EFSA assessment workflow for 90-day studies on the whole food/feed submitted under Regulation (EU) No 503/2013. It was explained that such studies are scrutinised by EFSA against legal requirements (i.e. adherence to OECD TG 408, to GLP requirements, to EFSA guidance documents, including the EFSA Statement 2014[2]) and that possible deviations are evaluated as regards their impact on the study results. It was clarified that this applies to 90-day studies provided in the context of single-event or stack-event dossiers (even if previously submitted and assessed), in line with Regulation (EU) No 503/2013. Questions may be asked to the applicant during the process, and the additional information is incorporated in the study assessment. Procedural considerations on the submission of 90-day studies specific to stack dossiers were also provided, including the possibility of

[1] Through Annex G of EFSA opinions.

[2] https://www.efsa.europa.eu/en/efsajournal/pub/3871

redundant questions under different applications considering the principle of stand-alone dossiers; that stepwise submission of studies is accepted and additional info is 'processed' as soon as received, irrespective of the dossier.

The presentation was followed by a general discussion. GMO Network experts from Belgium Bulgaria, the Netherlands, Czech Republic, Denmark, Germany, Ireland, Italy, and Poland expressed a wish for a discussion on the risk assessment aspects linked to the topic to be organised at a later time; Austria did not support this proposal. France suggested to perform some controls on information that is often missing in the applications (e.g. treatment with the intended herbicide, experimental design) during the completeness check, because there is not much added value for CAs to perform this kind of control. EFSA confirmed that such preparatory check is completed early in the risk assessment process, also taking advantage of preparatory work supported by a dedicated framework contract. The possibility to run this preparatory work during completeness check will be investigated in EFSA.

4.2 Technical Note on the quality of DNA sequencing for the molecular characterisation of genetically modified plants

Nikoletta Papadopoulou, scientific officer of the GMO Unit, presented to the GMO Network members the new Technical Note on the quality of DNA sequencing for the molecular characterisation of GM plants, which was published in July 2018. In 2017, the European Commission mandated EFSA to develop a technical note for the applicants on, and the checking of, the quality of the sequencing methodology, analysis and reporting when DNA sequencing technologies are used for the molecular characterisation of the GM plant, building on the JRC guideline of 2016 (updated April 2017)[3] related to the verification and quality assessment of the sequencing of the insert(s) and flanking regions. The EFSA technical note puts together requirements and recommendations for DNA sequencing when used for the characterisation of the inserted genetic material at each insertion site and flanking regions, the determination of the copy number of all detectable inserts, and the analysis of the genetic stability of the inserts, when addressed by Sanger sequencing or NGS. This Technical Note will replace the JRC guideline of 2016 (updated April 2017) for any new application submitted to EFSA after October 1st, 2018. This document does not take into consideration the verification and validation of the detection method which remains under the remit of the JRC. During the presentation, the Network members were informed about the implementation and data storage of large raw data files that are expected to be submitted with applications including Next Generation Sequencing (NGS) experiments.

GMO Panel members and EFSA staff addressed clarification questions from experts from Austria, France, Germany, and the Netherlands on technical aspects of sequencing (inverted repeat regions, depth of coverage) and discussed the context of the new Technical Note and its implementation. The Network members were asked whether they had the intention (based on technical capacity and resources) to analyse the raw NGS data that will be submitted in applications, which does not seem to be the case at present.

[3] http://gmo-crl.jrc.ec.europa.eu/doc/Guideline-Sequencing-Feb-2016-mod-April-2017.pdf

4.3 Explanatory note on the selection of forage material suitable for the risk assessment of GM feed of plant origin

Michele Ardizzone, scientific officer of the GMO Unit, presented to the GMO Network members the new Technical Note on the selection of forage material suitable for the risk assessment of GM feed of plant origin, which was published in January 2018. EFSA identified the need to provide further clarification on its Guidance for the risk assessment of food and feed from genetically modified plants. Regulation (EU) No 503/2013 requires, amongst others, data from raw agricultural commodities entering the feed production and processing chain. Different parts of a plant, i.e. whole grain, bean or seed and forage, may enter the feed chain as unprocessed raw material. Whereas the grain, bean and seed are well-defined for each plant, the definition of forage varies on a crop-by-crop basis as the parts likely to enter the feed chain differ among crops. This explanatory note provides a crop-specific definition of forage for maize, soybean, sugarbeet, rapeseed and cotton, mitigating the lack of forage definition in the regulatory context and supporting the appropriate selection of forage material, as required by Regulation (EU) No 503/2013.

Following a question from the Netherlands on the amount of forage imported in the EU, EFSA clarified that the assessment must cover all possible uses, independently of the amount of product imported. Jan Pedersen (Denmark) asked whether an applicant could limit the application to import of e.g. seeds and avoid the risk assessment of forage, to which EFSA replied that the risk assessment should cover all possible uses indicated by the scope of the application; a representative of the European Commission added that it is recommended to have a full-scope application. Jaroslava Ovesna (Czech Republic) asked whether the requirements of this explanatory note imply that applicants should provide more data, to which EFSA replied that the explanatory note clarifies and harmonises data production and, since it has been built on experience from applications, these requirements are already met by applicants in many cases. Emmanuelle Pic (France) asked whether submission of forage data is mandatory, following the publication of this explanatory note, to which EFSA replied positively, in the case of crops indicated in the explanatory note (i.e., soybean and maize).

4.4 Explanatory note on the determination of newly expressed protein levels in the context of genetically modified plant applications for EU market authorisation

Konstantinos Paraskevopoulos, scientific officer of the GMO Unit, presented the recently published explanatory note on the determination of newly expressed protein levels in the context of GM plant applications for EU market authorisation. An overview of the document was presented; this included: (i) the identified need (EFSA self-task) in producing this document and provide details on the key methodological aspects of the determination of newly expressed proteins (NEPs) levels that should be considered and reported by applicants in order to harmonise the information in GM plant applications submitted to EFSA (ii); the terms of reference and data/methodologies, highlighting that legislation, guidance documents, scientific literature, bioanalytical method validation documents, as well as gained experience from already assessed EFSA GM plant applications were taken into account; (iii) the main content describing the two principal aspects of a targeted protein quantification methodology, i.e. sample

preparation/extraction of the NEP(s), and the analytical method employed to quantify the NEP(s), including the elements regarding the validation of the chosen experimental approach; (iv) recommendations for the description and reporting of the methodology used and data obtained. It was also highlighted that the document is not intended to recommend any specific experimental approach.

Annikki Welling (Finland) asked about the approach to be followed when an endogenous protein is present at higher levels due to the genetic modification, to which EFSA replied that if the risk assessment identifies an endogenous protein to be analysed, the principles of the explanatory note should be applied. Emmanuelle Pic (France) mentioned that based on feedback from the experts of ANSES' GMO Panel, there was a risk for an increase in the work needed to assess data on NEP levels determination. EFSA replied that this explanatory note is meant to assist applicants in providing data for which EFSA had to routinely ask additional questions in the past; by having more complete data packages, this should also reduce the work of assessors, both at EFSA and MS level. EFSA also offered to provide practical assistance (if needed) on the NEP levels data assessment when the applications are submitted for which the explanatory note will be applicable.

4.5 Human dietary exposure assessment

José Ángel Gómez Ruiz, scientific officer of the GMO Unit, gave a presentation on human dietary exposure to endogenous and new constituents in the area of GM food describing how it fits in the risk assessment of GM food. The presentation was based on a technical note being prepared by the GMO Unit to provide guidance to applicants on how human dietary exposure should be carried out and which information they need to provide to EFSA for its assessment. This technical note is needed, since the information currently provided by the applicants on dietary exposure is heterogeneous and sometimes incomplete. The presentation also described how applicants should make use of the available data, both concentration data in raw primary commodities and food consumption data. An overview was also given on different on-going projects in EFSA that could have an impact on dietary exposure assessment in the GMO area, with special attention to the raw primary commodity (RPC) model that pursues the conversion of the consumption data on processed foods present in the EFSA Comprehensive Consumption database into raw commodities using different recipes and factors. Main sources of uncertainty on the estimation of dietary exposure were summarised indicating the main areas where this uncertainty could be reduced.

Emmanuelle Pic (France) enquired whether this explanatory note will go through public consultation, to which EFSA replied that, since this is a technical document, such a phase is not foreseen.

9 November 2018

5. Welcome and apologies for absence

The Chair welcomed the participants and explained that the topics of this day are linked to recently received mandates form the EC on Gene Drive and Synthetic Biology, respectively. In these mandates, EFSA is requested to review

relevant EFSA guidelines for their adequacy in light of the new developments. EFSA has initiated the work and very much welcomes the possibility to exchange with the GMO network members on the topics.

6. Topics for discussion

6.1 Monitoring of synthetic biology by the ZKBS

Wilfried Wackernagel, professor at the University of Oldenburg, Germany, presented an overview of the monitoring activities on synthetic biology by the German Central Committee on Biological Safety (ZKBS). Synthetic Biology (SynBio) is a rapidly growing research field worldwide. In the absence of a broadly accepted definition, SynBio was considered in this presentation as a scientific concept in which engineering design practice is applied to the construction of biological systems and cells at the genetic, biochemical, and physiological level for novel applications. The various research activities are grouped into five subfields presented along with examples: 1. Synthesis of genes and genomes, 2. Design of genetic signalling circuits, 3. Metabolic engineering, 4. Minimal cells: genome reduction and protocells, 5. Xenobiology. In contrast, research on gene drives is not considered part of SynBio. In Germany, the government has commissioned in 2009 the monitoring of SynBio to the ZKBS, with emphasis on identifying risks for biosafety in the subfields of SynBio and whether or not the risk assessment methods for GMOs are applicable in these instances. According to the ZKBS, the major part of research on SynBio and its products is covered by the European GMO regulations but there are instances where the risk assessment criteria set forth in the GMO regulations are not applicable. The progress in these areas of SynBio is assessed with a case-by-case approach and might require an extended risk assessment in the future.

Boet Glandorf (the Netherlands) asked whether SynBio applications are assessed as GMOs in Germany, to which Prof. Wackernagel replied that the assessment is done on a case-by-case basis.

6.2 Similarities and differences between classical GMO and Gene Drive Organisms – challenges for the risk assessment

Samson Simon, scientist at the German Federal Agency for Nature Conservation (BfN), gave a presentation on gene drive organisms. Synthetic gene drive organisms (GDO) clearly represent genetically modified organisms (GMO) according to EU legislation. Important differences between current GMO and GDO which have profound consequences for the risk assessment have been identified. Those differences include a strategy change in goals for GDO, the requirement of GDO to spread the genetic modification, the inheritance of the laboratory tools in the wild for CRISPR gene drives, the modification of wildlife with consequences for many species, food webs, and ecosystems, and the potential of GDO to create public goods. As a consequence, the environmental risk assessment (ERA) of GDO has to consider novel features which add to present challenges. Those include, but are not limited to, gaps in biological data and undefined limits of concern for environmental risks, and a lack of comparators. On a more general level, ethical and socioeconomic considerations have to be taken into account. To assist the ERA, BfN recently initiated an R&D project on the risk assessment of synthetic gene drive systems. The project will cover available methods related to the risk assessment, including modelling, to enable evaluation of efficacy of gene drives, determination of data requirements

and modelling for environmental risk assessment, as well as specific and novel requirements for monitoring.

The presentation was followed by a general discussion. Nenad Malenica (Croatia) asked about the long-term effects of GDOs, to which Dr. Simon replied that this field is still young and the environmental consequences are indeed important to consider. Boet Glandorf (the Netherlands) suggested that sterile GM insects may serve as a good comparator for the assessment, and Dr. Simon concurred, with the mention that this would not be applicable for all types of GD insects. Catherine Golstein (France) referred to the 2017 Haut Conseil des Biotechnologies report on GM mosquitoes for vector control and indicated that specific cases should be assessed, to which Dr. Simon replied that the BfN has started working also on specific cases.

6.3 Assessment of human health and environmental risks of new developments in modern biotechnology

Boet Glandorf, scientist at the Netherlands National Institute for Public Health and the Environment (RIVM) and member of the GMO Network, presented a report on the assessment of human health and environmental risks of new developments in modern biotechnology. Due to rapid developments in modern biotechnology, many new applications are expected in the next ten years. To be prepared, RIVM has developed a framework to assess whether the current risk assessment method for human health and the environment is still adequate. This framework was applied to a selection of nearly thirty new applications. The current risk assessment method appears to be adequate for about half of these. For the other half, the risk assessment method may no longer be adequate, or insufficient knowledge or information is available to effectively assess risks. In the present study the risk assessment method for genetically modified organisms was reviewed. This method is used for living organisms whose genetic material has been modified, as has been the case for most current biotechnology applications. It is concluded that in order to deal with the expected bottlenecks in the current risk assessment, there is a need to draw lessons from other risk assessment methods, to gather existing information and knowledge and to fill knowledge gaps.

The presentation was followed by a general discussion. Against the background that genetic modification of animals and insects as well as gene drive applications were separately specified in the presentation, Andrea Scheepers (Germany) asked whether also potential gene drive applications in (small) domesticated animals were considered or whether the conclusions of the report regarding gene drive only refer to the given example of gene drive applications for insect population reduction/modification. Dr. Glandorf affirmed the latter and stated that the report focused on applications that will come to the market in the near future, which is not the case for domestic animals; she added that most of the developments concern insects. EFSA inquired on the sources of information for this report and the criteria used to define categories and allocate applications to each of them, to which Dr. Glandorf replied that the report is mainly based on expert judgement.

6.4 General discussion – Tour de table to collect information on activities conducted by Member States on synthetic biology and gene drive

EFSA invited Member State experts to share information on their work (finalised, currently on-going or planned for the future) on synthetic biology and gene drive. Experts from Austria, Finland, France, Germany, Greece, the Netherlands, Norway, Slovenia, Sweden, and Switzerland responded and described their work in these areas.

The experts were also asked about their views on applications that would be plausible for the near future and which case-studies would be useful in guiding the exercise, considering that the definitions given in the mandate were quite broad. Several examples were given by the Network experts: plants modified to influence the microbiome, microorganisms used for biocontrol on plants, microorganisms used as fertilisers, microorganisms producing plastic used for food packaging.

Another point of the discussion was how the size and number of modifications inserted could affect the risk assessment of the organisms in question; Boet Glandorf (the Netherlands) indicated that, in those cases, her institute uses bioinformatics to determine the impact the multiple sequence changes on the function of the protein.

7. Any Other Business

7.1 Date of next meeting

Irina Olaru, scientific officer of the GMO Unit, indicated that possible dates for the 2019 meeting are currently under assessment; likely candidates are the third week of June and the interval between 7 October and 15 November. The final date will be communicated in due time.

7.2 Upcoming events

Irina Olaru also informed the audience that the GMO Panel will hold an open plenary meeting in 2019, to which GMO Network members are encouraged to register as observers. The date of the open meeting will be communicated, once fixed.

8. Conclusions

The Chair summarised the actions to be taken after the meeting, related to the adoption of the minutes, the preparation of guidelines for MS comments on GMO applications, and the communication to EFSA of information (documents or links to documents and activities) on gene drive and synthetic biology that have been or are being performed in the MS.

The Chair 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 EFSA staff for organising and contributing to the meeting.

9. Closure of the meeting